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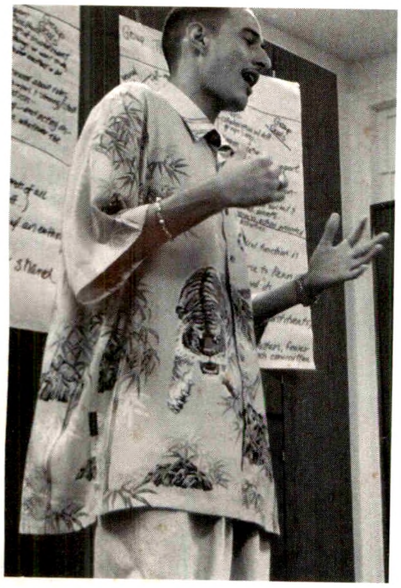

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NEW
FDA Approved
for Acute Pain and
Primary Dysmenorrhea in Adults

Xperience

ESTABLISHED EFFICACY

- Rapid,* sustained relief of OA[1]
- Powerful, sustained relief of adult RA[2]

EXCELLENT TOLERABILITY

- Upper GI tolerability comparable to placebo[3,4]

TRUSTED SAFETY

- No dose-related increase in hypertension or peripheral edema[1]

The #1 prescribed arthritis brand†

CELEBREX®
(CELECOXIB CAPSULES) 100 mg 200 mg

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TEAM SUPPORTER
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CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib; in patients who have demonstrated allergic-type reactions to sulfonamides; and in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.

Serious GI toxicity such as bleeding, ulceration, and perforation can occur with or without warning symptoms in patients treated with NSAIDs.

Most common side effects were dyspepsia (8.8% vs 6.2% for placebo), diarrhea (5.6% vs 3.8% for placebo), and abdominal pain (4.1% vs 2.8% for placebo), and were generally mild to moderate.

As with all NSAIDs, CELEBREX should be used with caution in patients with fluid retention, hypertension, or heart failure. NSAIDs may diminish the effects of ACE inhibitors and can reduce the natriuretic effect of furosemide and thiazides.

CELEBREX should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. CELEBREX should be avoided during late pregnancy.

*Significant relief in 24 to 48 hours.

†IMS America. National Prescription Audit. September, 2001.

Please see brief summary of prescribing information and references on next page.

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(P24749

CELEBREX®
(celecoxib capsules)

Brief summary of prescribing information.

INDICATIONS AND USAGE

For relief of the signs and symptoms of osteoarthritis (OA), and of rheumatoid arthritis (RA) in adults. For the management of acute pain in adults. For the treatment of primary dysmenorrhea.

CONTRAINDICATIONS

CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib. CELEBREX should not be given to patients who have demonstrated allergic-type reactions to sulfonamides or to those who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS — Anaphylactoid Reactions, and PRECAUTIONS — Preexisting Asthma).

WARNINGS

Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation: Serious GI toxicity (bleeding, ulceration, and perforation of the stomach, small intestine or large intestine) can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Inform patients about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, occur in about 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. It is presently unclear how the above rates apply to CELEBREX . Among 5,285 patients who received CELEBREX in controlled clinical trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 200 mg or more, 2 (0.04%) experienced significant upper GI bleeding, at 14 and 22 days after initiation of dosing. About 40% of these 5,285 patients were in studies that required them to be free of ulcers by endoscopy at study entry. Thus it is unclear if this study population is representative of the general population. Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking CELEBREX vs. comparator NSAID products have not been performed. Prescribe NSAIDs with extreme caution in patients with a prior history of ulcer disease or GI bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore take special care in treating this population. **To minimize the potential risk for an adverse GI event, use the lowest effective dose for the shortest possible duration.** For high risk patients, consider alternate therapies that do not involve NSAIDs. Studies have shown that patients with a *prior history of peptic ulcer disease and/or GI bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. Pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX. In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS — Preexisting Asthma). Seek emergency help in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease: Treatment with CELEBREX is not recommended, but if it is used, monitoring of kidney function is advised.

Pregnancy: Avoid CELEBREX in late pregnancy because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General: CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Hepatic Effects: Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (about three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These lab abnormalities may or may not change with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including CELEBREX. In controlled clinical trials of CELEBREX, the incidence of borderline elevations of liver tests was 6% for CELEBREX and 5% for placebo, and about 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX. Discontinue CELEBREX if clinical signs and symptoms of liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash).

Renal Effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, or liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs. Use caution when initiating treatment with CELEBREX in patients with considerable dehydration. Rehydrate patients first and then start therapy with CELEBREX. Use caution in patients with pre-existing kidney disease (see WARNINGS — Advanced Renal Disease).

Hematological Effects: In controlled clinical trials the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages.

Fluid Retention and Edema: Fluid retention and edema have been reported. Use CELEBREX with caution in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma: Do not use in patients with aspirin-sensitive asthma because of the risk of severe bronchospasm. Use with caution in patients with preexisting asthma.

Information for Patients: Inform patients of the following: GI bleeding which may result in hospitalization and fatal outcomes; to be alert for signs and symptoms of ulcerations and bleeding, and seek medical advice should these be observed; to promptly report GI ulceration or bleeding, skin rash, unexplained weight gain, or edema; to stop therapy and seek immediate medical help if they experience warning signs and symptoms of hepatotoxicity; to seek immediate emergency help in the case of an anaphylactoid reaction; and to avoid CELEBREX in late pregnancy.

Laboratory Tests: Because serious GI tract ulcerations and bleeding can occur without warning symptoms, monitor for signs or symptoms of GI bleeding. During controlled clinical trials, there was an increased incidence of hyperchloremia and other lab abnormalities including hypophosphatemia and elevated BUN in patients receiving celecoxib compared with patients on placebo. These lab abnormalities were also seen in patients who received comparator NSAIDs in these studies.

Drug Interactions: ***General:*** Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by P450 2D6. ***ACE-inhibitors:*** Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. ***Furosemide:*** Clinical studies, and post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. ***Aspirin:*** CELEBREX can be used with low dose aspirin; however, concomitant administration may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX alone. CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis. ***Fluconazole:*** Concomitant administration of fluconazole 200 mg QD resulted in a two-fold increase in celecoxib plasma concentration is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole. Initiate CELEBREX at the lowest recommended dose in patients receiving fluconazole. ***Lithium:*** Mean steady-state lithium plasma levels increased approximately 17% in healthy subjects receiving lithium 450 mg BID with CELEBREX 200 mg BID compared with those receiving lithium alone. Closely monitor patients on lithium when CELEBREX is introduced or withdrawn. ***Methotrexate:*** CELEBREX did not have a significant effect on the pharmacokinetics of methotrexate in rheumatoid arthritis patients. ***Warfarin:*** Monitor anticoagulant activity, particularly in the first few days, after initiating or changing therapy with CELEBREX in patients receiving warfarin or similar agents; these patients are at an increased risk of bleeding complications. In healthy subjects receiving daily doses of 2-5 mg of warfarin, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin. **Carcinogenesis, mutagenesis, impairment of fertility:** Celecoxib was not carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-fold the human exposure as measured by the AUC_{0-24} at 200 mg BID) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24} at 200 mg BID) for two years. Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an in vivo micronucleus test in rat bone marrow. Celecoxib did not impair male and female fertility in rats at oral doses up to 600 mg/kg/day (approximately 11-fold human exposure at 200 mg BID based on the AUC_{0-24}).

Pregnancy: ***Teratogenic effects:*** Pregnancy Category C. Celecoxib at oral doses ≥ 150 mg/kg/day (about 2-fold human exposure at 200 mg BID as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥ 30 mg/kg/day (about 6-fold human exposure based on the AUC_{0-24} at 200 mg BID) throughout organogenesis. There are no studies in pregnant women. Use CELEBREX during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Nonteratogenic effects:*** Celecoxib produced pre- and post-implantation losses and reduced embryo/fetal survival in rats at oral dosages ≥ 50 mg/kg/day (about 6-fold human exposure based on the AUC_{0-24} at 200 mg BID). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are they expected at clinical exposures. No human studies have been conducted on the effect of celecoxib on the closure of the ductus arteriosus. Use of CELEBREX during the third trimester of pregnancy should be avoided. **Labor and delivery:** Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (about 7-fold human exposure as measured by the AUC_{0-24} at 200 mg BID). The effects of CELEBREX on labor and delivery in pregnant women are unknown. **Nursing mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CELEBREX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated. **Geriatric Use:** While the incidence of adverse experiences tended to be higher in elderly patients, no substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out

ADVERSE REACTIONS

Adverse events occurring in ≥2% of Celebrex patients from controlled arthritis trials, regardless of causality at recommended doses (N=4146): abdominal pain 4.1%, diarrhea 5.6%, dyspepsia 8.8%, flatulence 2.2%, nausea 3.5%, back pain 2.8%, peripheral edema 2.1%, injury-accidental 2.9%, dizziness 2.0%, headache 15.8%, insomnia 2.3%, pharyngitis 2.3%, rhinitis 2.0%, sinusitis 5.0%, upper respiratory tract infection 8.1%, rash 2.2%. 7.1% of patients receiving CELEBREX and 6.1% for placebo discontinued due to adverse events in placebo or active controlled clinical trials. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (0.8% and 0.7%, respectively). Among placebo patients, 0.6% discontinued due to dyspepsia and 0.6% due to abdominal pain. The following adverse events occurred in 0.1-1.9% of patients regardless of causality.

Celebrex (100-200 mg BID or 200 mg QD): GI: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting; ***Cardiovascular:*** Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction; ***General:*** Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain; ***Resistance mechanism disorders:*** Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media; ***Central, peripheral nervous system:*** Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo; ***Female reproductive:*** Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis; ***Male reproductive:*** Prostatic disorder; ***Hearing and vestibular:*** Deafness, ear abnormality, earache, tinnitus; ***Heart rate and rhythm:*** Palpitation, tachycardia; ***Liver and biliary system:*** Hepatic function abnormal, SGOT increased, SGPT increased; ***Metabolic and nutritional:*** BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase; ***Musculoskeletal:*** Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis; ***Platelets (bleeding or clotting):*** Ecchymosis, epistaxis, thrombocythemia; ***Psychiatric:*** Anorexia, anxiety, appetite increased, depression, nervousness, somnolence; ***Hemic:*** Anemia; ***Respiratory:*** Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia; ***Skin and appendages:*** Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria; ***Application site disorders:*** Cellulitis, dermatitis contact, injection site reaction, skin nodule; ***Special senses:*** Taste perversion; ***Urinary system:*** Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection; ***Vision:*** Blurred vision, cataract, conjunctivitis, eye pain, glaucoma.

Other serious adverse reactions which occur rarely (estimated < 0.1%), regardless of causality: Cases reported only in the post-marketing experience are indicated in italics. ***Cardiovascular:*** Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, *vasculitis;* ***GI:*** Intestinal obstruction, intestinal perforation, GI bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus; ***Liver and biliary system:*** Cholelithiasis, *hepatitis, jaundice, liver failure;* ***Hemic and lymphatic:*** Thrombocytopenia, *agranulocytosis, aplastic anemia, pancytopenia, leukopenia;* ***Metabolic:*** *Hypoglycemia;* ***Nervous system:*** Ataxia, suicide; ***Renal:*** Acute renal failure, *interstitial nephritis;* ***Skin:*** *Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis;* ***General:*** Sepsis, sudden death, *anaphylactoid reaction, angioedema.*

Adverse events from analgesia and dysmenorrhea studies: About 1,700 patients were treated with CELEBREX in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies received a single dose of study medication. Doses up to 600 mg/day of CELEBREX were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies. In about 700 patients treated with CELEBREX in the post-general and orthopedic surgery pain studies, the most commonly reported adverse events were nausea, vomiting, headache, dizziness and fever.

OVERDOSAGE

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. GI bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. Manage patients by symptomatic and supportive care following an overdose. There are no specific antidotes. Dialysis is unlikely to be useful. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful.

DOSAGE AND ADMINISTRATION

Osteoarthritis - 200 mg QD or 100 mg BID.

Rheumatoid arthritis - 100 or 200 mg BID.

Acute Pain and Primary Dysmenorrhea - 400 mg initially followed by an additional 200 mg dose if needed on the first day. On subsequent days, 200 mg BID.

Hepatic Insufficiency: Reduce daily dosage by 50% for patients with moderate hepatic impairment (Child-Pugh Class II).

Rx only

Manufactured for:
G.D. Searle LLC
A subsidiary of Pharmacia Corporation
Chicago, IL 60680, USA
Pfizer Inc.,
New York, NY 10017, USA

by:
Searle Ltd.
Caguas, PR 00725

celb1001.b1109 B-1-S

References: 1. Data on file. Searle, a subsidiary of Pharmacia. **2.** Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA*. 1999;282:1921-1928. **3.** Bensen WG, Zhao SZ, Burke TA, et al. Upper gastrointestinal tolerability of celecoxib, a COX-2 specific inhibitor, compared to naproxen and placebo. *J Rheumatol.* 2000;27:1876-1883. **4.** Bensen WG, Agrawal NM, Zhao SZ, et al. Upper gastrointestinal (UGI) tolerability of celecoxib, a COX-2 specific inhibitor, compared to naproxen and placebo [abstract]. Program and abstract of the American College of Rheumatology; November 13-17, 1999; Boston, Mass. Abstract 430.

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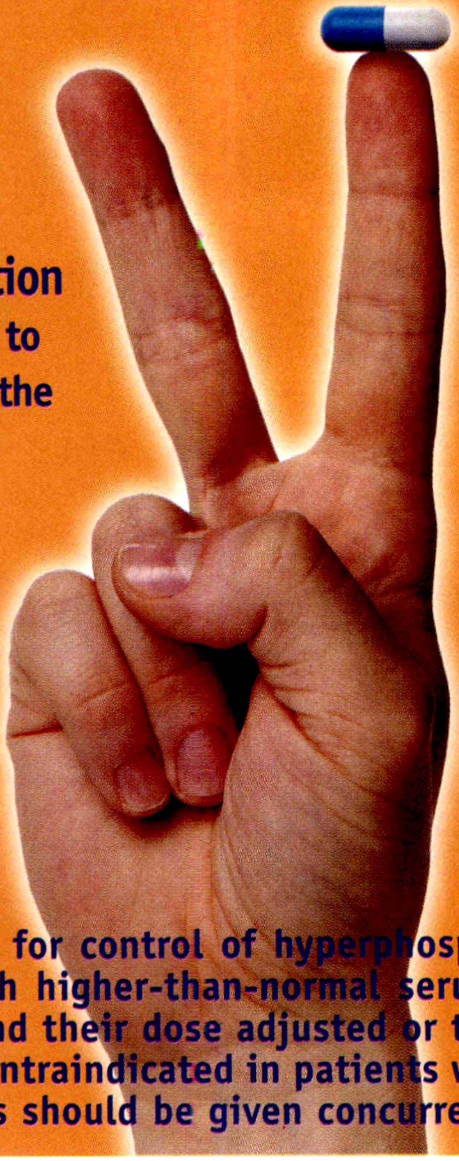
Concerned about calcium absorption with your calcium phosphate binder?

Two Reasons To Choose PhosLo® Over Calcium Carbonate



1/2

as much Ca absorption with PhosLo compared to calcium carbonate at the same calcium dose[1]

2x

more PO_4 binding with PhosLo compared to calcium carbonate at the same calcium dose[2]

New
PhosLo®
GelCaps
(Calcium Acetate)
667 mg

PhosLo® is indicated for control of hyperphosphatemia in end-stage renal failure. Patients with higher-than-normal serum calcium levels should be closely monitored and their dose adjusted or terminated to bring levels to normal. PhosLo is contraindicated in patients with hypercalcemia. No other calcium supplements should be given concurrently with PhosLo.

Brief Summary: Before prescribing, see complete prescribing information. **Contraindications:** Patients with hypercalcemia. **Indications and Usage:** PhosLo is indicated for the control of hyperphosphatemia in end stage renal failure and does not promote aluminum absorption. **Warnings:** Patients with end stage renal failure may develop hypercalcemia when given calcium with meals. No other calcium supplements should be given concurrently with PhosLo. Progressive hypercalcemia due to overdose of PhosLo may be severe as to require emergency measures. Chronic hypercalcemia may lead to vascular calcification, and other soft-tissue calcification. The serum calcium level should be monitored twice weekly during the early dose adjustment period. **The serum calcium times phosphate (CaXP) product should not be allowed to exceed 66.** Radiographic evaluation of suspect anatomical region may be helpful in early detection of soft-tissue calcification. **Precautions:** Excessive dosage of PhosLo induces hypercalcemia; therefore, early in the treatment during dosage adjustment serum calcium should be determined twice weekly. Should hypercalcemia develop, the dosage should be reduced or the treatment discontinued immediately depending on the severity of hypercalcemia. PhosLo should not be given to patients on digitalis, because hypercalcemia may precipitate cardiac arrhythmias. PhosLo therapy should always be started at low dose and should not be increased without careful monitoring of serum calcium. An estimate of daily calcium intake should be made initially and the intake adjusted as needed. Serum phosphorus should also be determined periodically. PhosLo should be taken with meals to insure the mixing of calcium with dietary phosphate. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long term animal studies have not been performed to evaluate the carcinogenic potential, mutagenicity, or effect on fertility of PhosLo. **Pregnancy:** Teratogenic Effects: Category C. Animal reproduction studies have not been conducted with PhosLo. It is not known whether PhosLo can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PhosLo should be given to a pregnant woman only if clearly needed. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of subjects in clinical studies of PhosLo (n = 91), 25 percent were 65 and over, while 7 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Adverse Reactions:** In clinical studies, patients have occasionally experienced nausea during PhosLo therapy. Hypercalcemia may occur during treatment with PhosLo. Mild hypercalcemia (Ca>10.5 mg/dl) may be asymptomatic or manifest itself as constipation, anorexia, nausea and vomiting. More severe hypercalcemia (Ca>12 mg/dl) is associated with confusion, delirium, stupor and coma. Mild hypercalcemia is easily controlled by reducing the PhosLo or temporarily discontinuing therapy. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing PhosLo therapy. Decreasing dialysate calcium concentration could reduce the incidence and severity of PhosLo induced hypercalcemia. The long-term effect of PhosLo on the progression of vascular or soft-tissue calcification has not been determined. Isolated cases of pruritus have been reported which may represent allergic reactions. **Drug Interactions:** PhosLo may decrease the bioavailability of tetracyclines.

References: 1. Sheikh MS, Maguire JA, Emmett M, et al. Reduction of dietary phosphorus absorption by phosphorus binders. *J Clin Inves.* 1989;83:66-73.
2. Mai ML, Emmett M, Sheikh MS, et al. Calcium acetate, an effective phosphorus binder in patients with renal failure. *Kidney Int.* 1989:36:690-695.

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Phos-0013 December, 2001

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ARTICLES

Low-Dose Prednisone Therapy for Patients with Early Active Rheumatoid Arthritis: Clinical Efficacy, Disease-Modifying Properties, and Side Effects. A Randomized, Double-Blind, Placebo-Controlled Clinical Trial 1

A.A. van Everdingen, J.W.G. Jacobs, D.R. Siewertsz van Reesema, and J.W.J. Bijlsma

Prednisone, 10 mg/d, provides clinical benefit, particularly in the first 6 months, and substantially inhibits progression of radiologic joint damage in patients with early active rheumatoid arthritis and no previous treatment with disease-modifying antirheumatic drugs. Because of their limited disease-modifying effects, glucocorticoids should be combined with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis.

Summary for Patients I-26

Risk Factors for *Helicobacter pylori* Resistance in the United States: The Surveillance of *H. pylori* Antimicrobial Resistance Partnership (SHARP) Study, 1993–1999 13

J.M. Meyer, N.P. Silliman, W. Wang, N.Y. Siepman, J.E. Sugg, D. Morris, J. Zhang, H. Bhattacharyya, E.C. King, and R.J. Hopkins

Clinicians should consider risk factors for antimicrobial resistance when deciding which patients should have susceptibility testing and when choosing appropriate *Helicobacter pylori* treatments in the empirical setting.

Summary for Patients I-39

Recovery Rate and Prognosis in Older Persons Who Develop Acute Lung Injury and the Acute Respiratory Distress Syndrome 25

E.W. Ely, A.P. Wheeler, B.T. Thompson, M. Ancukiewicz, K.P. Steinberg, and G.R. Bernard, for the Acute Respiratory Distress Syndrome Network

Although the survival rate among mechanically ventilated patients 70 years of age or older in this study was high, these patients were twice as likely to die of acute lung injury compared with their younger counterparts, even after adjustment for covariates. Older survivors recovered from respiratory failure and achieved spontaneous breathing at the same rate as younger patients but had greater difficulty being liberated from the ventilator and being discharged from the intensive care unit.

Summary for Patients I-42

BRIEF COMMUNICATION

Anomalies of the Inferior Vena Cava in Patients with Iliac Venous Thrombosis 37

A. Obernosterer, M. Aschauer, W. Schnedl, and R.W. Lipp

An anomaly of the inferior vena cava should be suspected if thrombosis involving the iliac veins occurs in patients 30 years of age or younger. Patients with an anomaly and thrombosis may be at higher risk for thrombotic recurrence.

Summary for Patients I-46

ACADEMIA AND CLINIC

The Risk–Benefit Profile of Commonly Used Herbal Therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava 42

E. Ernst

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Caring for Patients at the End of Life: Reflections after 12 Years of Practice 72

R.A. Parker

The author describes interactions with families of dying patients, discusses logistic issues around dying, examines do-not-resuscitate orders, and highlights experiences with home visits.

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EDITORIAL

Are Long-Term Very Low Doses of Prednisone for Patients with Rheumatoid Arthritis as Helpful as High Doses Are Harmful? 76

T. Pincus, T. Sokka, and C.M. Stein

The elegantly designed and well-executed study by van Everdingen and colleagues in this issue presents a unique opportunity to evaluate benefits and risks of corticosteroid therapy for rheumatoid arthritis independent of other therapies; this clinical setting is unlikely to recur. It is commendable that these authors chose to reanalyze a therapy that has been available for more than 50 years.

POSITION PAPER

Pharmacist Scope of Practice 79

American College of Physicians–American Society of Internal Medicine

This paper explores the increased scope of practice of U.S. pharmacists; presents background information on the pharmacy profession, and outlines how the medical profession can work with pharmacists to enhance patient safety and quality of care.

LETTERS

Osteoarthritis: New Insights 86

T.E. Lindow; D.D. Waddell; P.J. Rosch; R.H. Palmer; D.T. Felson and T. McAlindon

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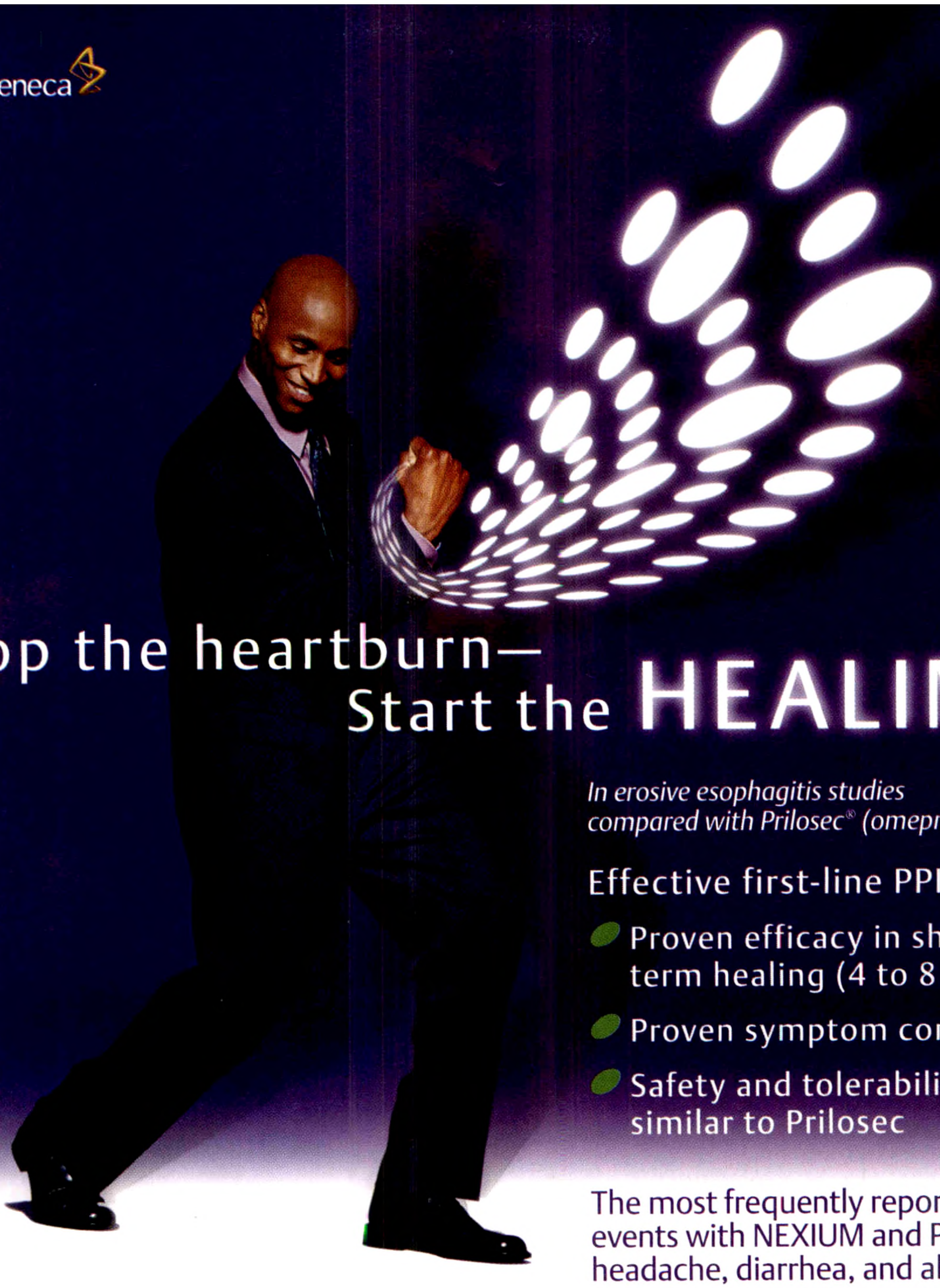

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The most frequently reported adverse events with NEXIUM and Prilosec are headache, diarrhea, and abdominal pain. Symptomatic response to therapy does not preclude the presence of gastric malignancy.

NEXIUM and Prilosec should be used only for the conditions, dosages, and durations specified in the Prescribing Information. Before prescribing NEXIUM or Prilosec, please see brief summary of full Prescribing Information on next page.

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20-MG, 40-MG Delayed-Release Capsules

BRIEF SUMMARY Before prescribing NEXIUM, please see full Prescribing Information. **INDICATIONS AND USAGE** NEXIUM is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. **CONTRAINDICATIONS** NEXIUM is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles. **PRECAUTIONS** Symptomatic response to therapy with NEXIUM does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which NEXIUM is an enantiomer. **Information for Patients:** NEXIUM Delayed-Release Capsules should be taken at least one hour before meals. For patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the capsule opened, and the pellets carefully emptied onto the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellet/applesauce mixture should not be stored for future use. Antacids may be used while taking NEXIUM. **DRUG INTERACTIONS** Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. *In vitro* and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin. Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole-metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of diazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance. Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole. Esomeprazole inhibits gastric acid secretion, therefore, it is theoretically possible that esomeprazole and omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg, ketoconazole, ampicillin esters, digoxin, and iron salts). **Carcinogenesis, Mutagenesis, Impairment of Fertility:** The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times the human dose of 20 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 5.6 times the human dose on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test. Omeprazole was positive in the *in vitro* human lymphocyte chromosome aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals. **Pregnancy:** *Teratogenic Effects. Pregnancy Category B* - Teratology studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Teratology studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.5 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human doses on a body surface area basis). There are no adequate and well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. **Nursing Mothers:** The excretion of esomeprazole in milk has not been studied. However, omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. Because esomeprazole and omeprazole are likely to be excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from esomeprazole and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of patients who received NEXIUM in clinical trials, 778 were 65 to 74 years of age and 124 patients were ≥ 75 years of age. No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **ADVERSE REACTIONS** The safety of NEXIUM was evaluated in over 10,000 patients (aged 18-84 years) in clinical trials worldwide including over 7,400 patients in the United States and over 2,600 patients in Europe and Canada. Over 2,900 patients were treated in long-term studies for up to 6-12 months. In general, NEXIUM was well tolerated in both short- and long-term clinical trials. The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1,240 patients on NEXIUM 20 mg, 2,434 patients on NEXIUM 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse events (≥1%) in all three groups was headache (5.5, 5.0, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking NEXIUM or omeprazole. Additional adverse events that were reported as possibly or probably related to NEXIUM with an incidence < 1% are listed below by body system: ***Body as a Whole:*** abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, chest pain substernal, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors; ***Cardiovascular:*** flushing, hypertension, tachycardia; ***Endocrine:*** goiter; ***Gastrointestinal:*** bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms NOS, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting; ***Hearing:*** earache, tinnitus; ***Hematologic:*** anemia, anemia hypochromic, cervical lymphoadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia; ***Hepatic:*** bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased; ***Metabolic/Nutritional:*** glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease; ***Musculoskeletal:*** arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica; ***Nervous System/Psychiatric:*** anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect; ***Reproductive:*** dysmenorrhea, menstrual disorder, vaginitis; ***Respiratory:*** asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis; ***Skin and Appendages:*** acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria; ***Special Senses:*** otitis media, parosmia, taste loss, taste perversion; ***Urogenital:*** abnormal urine, albuminuria, cystitis, dysuria, fungal infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria; ***Visual:*** conjunctivitis, vision abnormal. Endoscopic findings that were reported as adverse events include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration. Other adverse events not observed with NEXIUM, but occurring with omeprazole can be found in the omeprazole package insert. **OVERDOSAGE** A single oral dose of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions. There have been no reports of overdose with esomeprazole. Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert-**ADVERSE REACTIONS**). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive. As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

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PRiLOSEC®
(OMEPRAZOLE)

20-MG Delayed-Release Capsules

BRIEF SUMMARY Before prescribing PRILOSEC, please see full Prescribing Information. **INDICATIONS AND USAGE** *Erosive Esophagitis:* PRILOSEC Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) in the healing of erosive esophagitis, which has been diagnosed by endoscopy. **CONTRAINDICATIONS Omeprazole** PRILOSEC Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation. **PRECAUTIONS** Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy. Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole. **Information for Patients:** PRILOSEC Delayed-Release Capsules should be taken before eating and should not be opened, chewed or crushed, and should be swallowed whole. **DRUG INTERACTIONS** *Other* Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (eg, cyclosporine, disulfiram, and benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with PRILOSEC. Omeprazole inhibits gastric acid secretion, therefore, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg, ketoconazole, ampicillin esters, digoxin, and iron salts). In clinical trials, antacids were used concomitantly with the administration of PRILOSEC. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. Omeprazole was not mutagenic in an *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell assay and an *in vivo* rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an *in vivo* bone marrow chromosome aberration test. A second mouse micronucleus study at 2000 times the human dose, but with different (suboptimal) sampling times, was negative. In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals. **Pregnancy:** *Category C* - Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **ADVERSE REACTIONS** In the U.S. clinical trial population of 465 patients (including duodenal ulcer, Zollinger-Ellison syndrome and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients on therapy with PRILOSEC. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug:

	Omeprazole (n=465)	Placebo (n=64)	Ranitidine (n=195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

The following adverse reactions which occurred in 1% or more of omeprazole-treated patients have been reported in international double-blind, and open-label, clinical trials in which 2,631 patients and subjects received omeprazole and 120 patients took a placebo. A causal relationship was not assessed. The percentages are given omeprazole then placebo, respectively. *Body as a Whole, site unspecified:* Abdominal Pain 5.2% and 3.3%; Asthenia 1.3% and 0.8%. *Digestive System:* Constipation 1.5 and 0.8; Diarrhea 3.7 and 2.5; Flatulence 2.7 and 5.8; Nausea 4.0 and 6.7; Vomiting 3.2 and 10.0; Acid regurgitation 1.9 and 3.3; *Nervous System/Psychiatric:* Headache 2.9 and 2.5. Additional adverse experiences occurring in < 1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to PRILOSEC was unclear. *Body As a Whole:* Allergic reactions, including, rarely, anaphylaxis (see also *Skin* below), fever, pain, fatigue, malaise, abdominal swelling. *Cardiovascular:* Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema. *Gastrointestinal:* Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued. Gastroduodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with PRILOSEC. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors. *Hepatic:* Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy. *Metabolic/Nutritional:* Hyponatremia, hypoglycemia, weight gain. *Musculoskeletal:* Muscle cramps, myalgia, muscle weakness, joint pain, leg pain. *Nervous System/Psychiatric:* Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia. *Respiratory:* Epistaxis, pharyngeal pain. *Skin:* Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis. *Special Senses:* Tinnitus, taste perversion. *Urogenital:* Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia. *Hematologic:* Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.

OVERDOSAGE Rare reports have been received of overdosage with omeprazole. Doses ranged from 320 mg to 900 mg (16-45 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, and dry mouth. Symptoms were transient, and no serious clinical outcome has been reported. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

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Reference: 1. Prescribing Information for NEXIUM.

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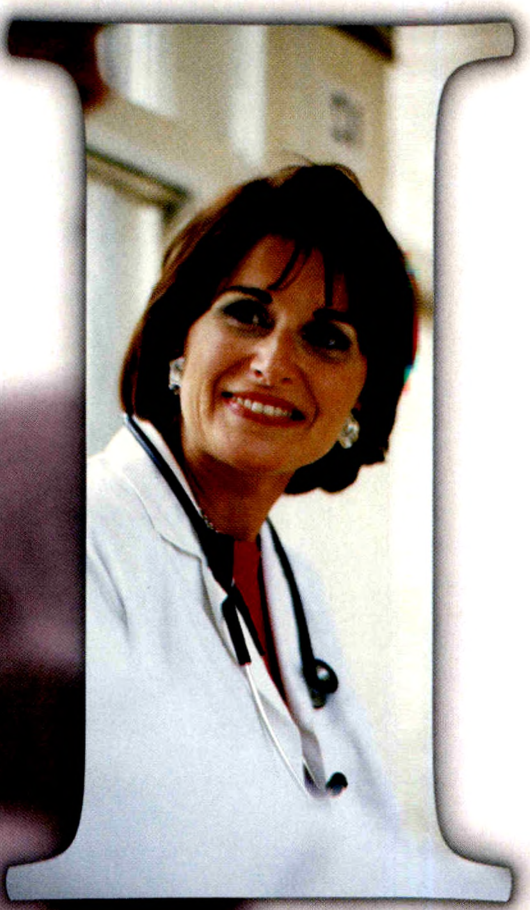

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5. Research protocols and supporting data, if applicable
6. Permissions
7. Comments from previous peer reviews (if any) and responses to these comments (optional)
8. The signed Authors' Forms—one for each author
9. The presubmission checklist
10. Reporting guideline checklist, if appropriate
11. Conflict of Interest forms (available at www.annals.org)

Cover Letter

Please submit the original and one photocopy of a cover letter indicating the *Annals* section (for example, Article, Brief Communication, Review) for which the submission would be most appropriate; the Editor makes the final assignment to a section (for a description of the formats of specific *Annals* articles, see the Appendix, appearing in the first issues of January and July each year and at www.annals.org)

The cover letter should also designate whether the corresponding author prefers to receive acknowledgment of receipt of the manuscript by U.S. mail, e-mail, telephone, or fax. For Letters to the Editor, the cover letter should clearly indicate whether the submitted Letter is intended for publication or is meant to be a communication to the Editor only. We encourage electronic submission of Letters to the Editor at www.acponline.org/shell-cgi/letter-article.pl. The cover letter should provide details of any duplicate submissions or of potential conflicts of interest disclosed on the author conflict of interest disclosures or on the conflict of interest notification page (see Conflict of Interest, under Authors' Professional and Ethical Responsibilities).

Manuscript

Submit a total of five paper copies as well as a copy on a diskette if you do not submit the manuscript electronically. This also applies to Letters to the Editor.

Figures

For black-and-white figures, submit five laser-quality proofs. For photographic material that does not photocopy well (for example, photomicrographs or radiographs), submit three glossy prints. For color figures, submit one transparency and three color prints for each figure. Indicate on a label the name of the first author of the paper, the figure number, and an arrow to denote the top of the figure. Paste the label on the back of the figure. Do not mount figures on backing board. Number the figures in the order in which they appear in the text. Photomicrographs should have scale markers that indicate the degree of magnification. Feel free to submit color figures. We will publish them in color if we think that color reproduction serves the purpose of the article.

Related Publications

Include reprints of published papers, manuscripts of papers in press, or copies of abstracts that contain data that appeared in the submitted manuscript. This information will help the Editors to form a judgment about the degree of duplicate, redundant, or previous publication.

Supporting Data

Submit original or other supplemental data if, in the authors' opinions, they would help the Editors or reviewers understand and interpret the work. Authors should submit a copy of the original research protocol, if appropriate.

Personal Communications

Submit a letter granting permission to publish all quoted personal communications, if applicable.

Previous Reviews and Responses

If the authors have previously submitted a version of the manuscript to another journal, the authors may include comments from the peer reviewers and an indication of the responses to these comments. This is optional.

Authors' Forms

Send completed and signed Authors' Forms (one for each author) with the manuscript. All authors, except U.S. government employees whose work was done as part of their official duties, must transfer copyright to the American College of Physicians–American Society of Internal Medicine, publisher of *Annals*. Transfer of copyright signifies transfer of rights for print publication; electronic publication; production of reprints, facsimiles, microfilm, or microfiche; or publication in a language other than English. We usually grant permission on request and without

charge for authors to use portions of their works published in *Annals* for limited educational purposes and in other scholarly publications.

Presubmission Checklist

Before mailing the submission packet, authors should complete the general presubmission checklist and submit it with the manuscript. For expanded information, see the Appendix, appearing in the first issues of January and July each year and at www.annals.org. Send the manuscript, accompanied by all supporting materials, with adequate protection for figures, to

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We acknowledge all manuscripts and assign each a unique, confidential manuscript number. Please give this number only to other authors of the paper. We require the manuscript number to release information on the manuscript. We provide instructions for how the corresponding author (the only person to receive the necessary password) can check the status of their manuscript online (at www.annals.org).

Internal Review by Editors

At least one Editor and one Associate Editor read each manuscript. Together, they decide whether to send the paper to outside reviewers.

Peer Review

We send about 50% of submitted papers for peer review, usually to at least two reviewers. The Editors select reviewers from an electronic database of about 13 000 reviewers; we do not send a manuscript to a reviewer who is affiliated with the same institution as any of the authors. We grade the quality and promptness of reviews to help us identify high-quality reviewers. We ask reviewers to treat manuscripts as confidential communications and not to share their content with anyone (except colleagues whom they ask to assist in reviewing) or to use the content for their own purposes. We ask the reviewer to declare any potential conflicts of interest, such as personal ties to authors or to an enterprise with a vested interest in the topic of the manuscript, and not to copy manuscripts. Reviewers have 3 weeks to complete their review. We receive nearly all reviews within 4 weeks. Authors may indicate individuals that they do not want us to ask to be a reviewer, but they must justify their request in the cover letter.

Acceptance or Rejection

Annals can publish only a fraction of all papers submitted each year (approximately 15% of all submissions in 2001). We communicate our decisions on acceptance or rejection only by a letter from the Editors to the corresponding author. Almost all papers that we accept require some editorial or statistical revision before publication.

Criteria for Editorial Decisions

We judge manuscripts on the interest and importance of the topic, the intellectual and scientific strength, the clarity of the presentation, and relevance to *Annals* readers. We also consider the strength of the paper compared with other papers under review, the need for *Annals* to represent a balanced picture of internal medicine, and the number of accepted papers in the paper's category. Authors of original research and reviews should take pains to describe exactly how their findings add to the existing literature.

Return of Manuscripts

We do not return manuscripts that we do not accept unless the authors make a specific request in the cover letter (see Cover Letter, under Assembling and Submitting a Packet); we do return all original figures, photographs, and slides, as well as the Authors' Form. Otherwise, we destroy all copies of rejected manuscripts. We send the reviewers' comments to authors whether or not we accept the article.

Resubmission

On occasion, the Editors will reject an article but invite a resubmission that addresses specific concerns of the Editors. We aim to accept a high percentage (approximately two thirds to three quarters) of the articles that we reinvite, and we specify conditions that the authors must meet before we will accept a reinvited manuscript.

EXPEDITED REVIEW

We will consider manuscripts for expedited review and early publication if they are of very high quality, if they have findings that are likely to affect practice immediately, and if rapid publication would probably minimize adverse patient care consequences. If authors thinks that their manuscript warrants expedited review, they should contact Deputy Editor Dr. Cynthia Mulrow to discuss whether the manuscript meets our criteria. We anticipate that fewer than 10 manuscripts per year will meet these criteria.

In general, two Editors will judge whether a manuscript is eligible for expedited review. Authors must submit the manuscript electronically and state in the cover letter why they believe the manuscript warrants expedited review. This review process will take approximately 3 weeks. We will write to the author with any suggestions for revision no later than 1 month after we initially received the manuscript and expect that authors will return the revised manuscript within 2 weeks. If accepted, we will schedule the manuscript for publication immediately such that it appears in print within about 3 months. In some instances, expedited manuscripts will be published within approximately 1 month of acceptance on www.annals.org, with print publication 2 months later.

Letters

Beginning in 2002, *Annals* will categorize Letters as Research Letters (includes case reports and case series), Comments and Responses (comments on papers published in *Annals*), General Commentary, or Corrections. We will publish a limited selection of Letters in both the print

journal and electronically, and some will be published solely on the *Annals* Web site (www.annals.org). Authors must note in their cover letter whether they are willing to have their letter published electronically if it is not selected for print publication. Electronically published Letters will not be indexed by the National Library of Medicine for the present.

We strongly encourage authors to submit their letters electronically. Research letters must be fewer than 600 words and must be structured with the following sections: Background, Objective, Methods and Findings, Conclusion, and References (no more than 10). One table or figure may be included. Comments and Responses and General Commentary must be fewer than 300 words, have three or fewer authors, and cite five or fewer references. Comments must be received within 6 weeks of an article's publication. Authors' Responses must be received within 4 weeks of receiving comments.

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The Appendix for the Information for Authors is published in the first issues of January and July. Please refer to the Appendix for information on manuscript format, style (manuscript typing and assembly), headings in text, style guidelines, title page, abstract, methods and results, discussion and conclusions, references, footnotes, tables and figures, acknowledgments, and current mailing address), and publication (scheduling of papers and proofs, ordering reprints, and complimentary copies).

APPENDIX: INFORMATION FOR AUTHORS

MANUSCRIPT FORMAT

The content of *Annals* is organized into sections, each with its own format, as shown in the **Table**.

STYLE

Manuscript Typing and Assembly

Double-space all parts of the manuscript, including tables, figure legends, and references. Type manuscripts in capital and lowercase letters, printed on white bond paper, 216 × 279 mm (8.5 × 11 in) or ISO A4 (212 × 297 mm). Arrange components in the following order: title page, conflict of interest notification page, abstract, text, references, tables in numerical sequence, figure legends, and appendices (if any). Begin each section on a separate page. Number all pages consecutively, starting with the title page.

Use no more than three levels of headings in the text. Position all headings flush with the left margin. Clearly indicate the levels of headings by using the following typographic conventions. First-level headings: Capitalize initial letter, use boldface. Second-level headings: Capitalize initial letters, use regular type. Third-level headings: Capitalize initial letters use italics. Keep headings short (three or four words). Do not use abbreviations.

Style Guidelines

Guidance on grammar, punctuation, and scientific writing appear in the following sources:

Scientific Style and Format: The CBE Manual for Authors, Editors, and Publishers. 6th ed. New York: Cambridge Univ Pr; 1994.

Medical Style and Format: Huth EJ. Philadelphia: ISI Pr; 1987. Marketed by Williams & Wilkins, Baltimore, Maryland.

Abbreviations and Symbols

Do not use abbreviations unless absolutely necessary; do abbreviate long names of chemical substances and terms for therapeutic combinations, such as MOPP. Abbreviate names of tests and procedures that are better known by their abbreviations than by the full name (VDRL test, SMA-12). Abbreviate units of measurement when they appear with numerals (. . . measured in milliliters, but 10 mL). Use abbreviations in figures and tables to save space. Explain all abbreviations used in the figure legend or table footnote.

Units of Measurement

Use SI units throughout (1). When reporting values for such commonly studied components as cholesterol, C-peptide, glucose, thyroxine, and urea nitrogen, report the value in SI units with traditional units given in parentheses.

Proprietary and Generic Names

Use generic names for all drugs. You may refer to an instruments by its proprietary name; give the name and location of the manufacturers in parentheses in the text.

Title Page

The title page should give the main title and subtitle (if any). The title should be as brief as possible while conveying the essential features of the article's contents; keep in mind that electronic search engines often use the title to locate papers. If the study is a randomized trial, use a subheading to so state. The title page should list authors in the order in which they are to appear in the byline of the published article. In the case of group authorship, identify one or more authors who will have responsibility for the publication (see Authorship, under Authors' Professional and Ethical Responsibilities). Give the institutional affiliation for each author, financial support information, trial registry information, short or "running" title, contact information for corresponding author, contact information for author to receive reprint requests, and word count.

Abstracts

Abstracts should accompany all submissions. The word limit of the abstracts for all submissions other than Brief Communications is 250 words; the word limit for Brief Communications is 150 words. Authors of original research and of systematic review papers (2) should submit a structured abstract (3) organized into the following categories, as applicable:

Original Research

Background, Objective, Design, Setting, Patients, Intervention, Measurements, Results, Conclusions.

Cost-Effectiveness Studies

Background, Objective, Design, Data Sources, Target Population, Time Horizon, Perspective, Interventions, Outcome Measures, Results of Base-Case Analysis, Results of Sensitivity Analysis, Conclusions.

Systematic Reviews

Purpose, Data Sources, Study Selection, Data Extraction, Data Synthesis, Conclusions.

The terms used to describe the research design should conform to standard usage and definitions (4, 5).

Methods (Including Statistical Considerations) and Results

We strongly encourage authors to review the essentials of good statistical reporting (6, 7). Guidelines are now available for the reporting of essential elements of randomized, controlled trials (8); meta-analyses of randomized, controlled trials (9); observational studies (10); economic analyses (11); and adverse drug reactions (12). We expect authors of reports in one of these categories to include the elements included in the guidelines. Authors should obtain a copy of the appropriate checklist of elements, either from the references cited here or from the *Annals* Web site (www.annals.org), and should include with the manuscript a copy of the appropriate checklist indicating whether essential study elements were reported and where to find them in the manuscript. Authors of studies that use other experimental designs must use similar care in presenting information on methods and results. Authors must be willing and able to provide original study data if requested by the Editors.

Table. ***Annals* Manuscript Formats***

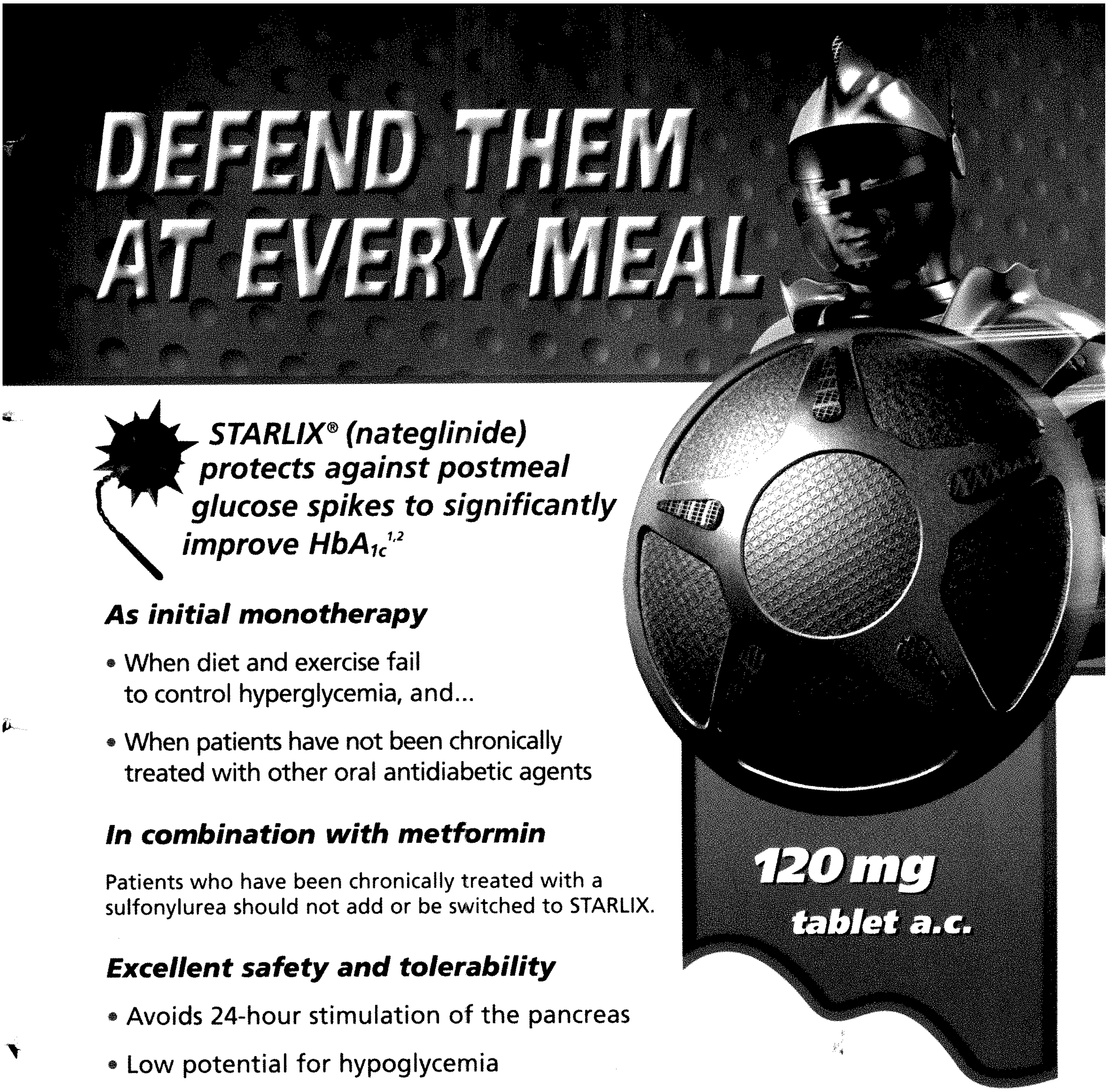
Section	Description	Word Limit	Type of Abstract†	Miscellaneous Considerations
Abroad	Reports on health care in countries other than the United States	2000	Unstructured	10 or fewer bibliographic references; 1 figure or table
Academia and Clinic	Descriptions and evaluations of innovations in concepts and procedures in medical education and training and in clinical practice	3200	Structured or Unstructured	
Ad Libitum	Prose and poetry	Prose limit: 900 words Poetry limit: 80 lines	NA	Should convey insight rather than opinion
Articles	Reports of original research on prevalence, causes, mechanisms, diagnosis, course, treatment, and prevention of disease. Rigorous systematic reviews and meta-analysis are included in this section	3200	Structured‡	Should follow standard reporting guidelines (e.g., CONSORT, MOOSE); total of 4 tables or figures
Brief Communications	Preliminary or limited results of original research on the causes, mechanisms, diagnosis, course, treatment, and prevention of disease	1500	Structured	20 or fewer bibliographic references; 2 figures or tables
Clinical Conferences	Edited transcripts of clinical conferences on basic and clinical topics	4000	Unstructured	
Editorials	Commentary on current topics or on papers published elsewhere in the issue	1000	NA	20 or fewer bibliographic references; no tables or figures; most editorials are solicited by the Editors
History of Medicine	Essays, reports, or biographic sketches on the evolution of medicine	3200	Unstructured	
In the Balance	Views on unsettled questions of diagnosis and treatment, particularly questions arising on common, important clinical problems	2000	Unstructured	Usually includes two papers presenting differing views and may be accompanied by an editorial; are often solicited by the Editors
Letters§	Comments and response on papers published in *Annals* and on other current topics and short research reports of clinical interest	Comments: 300 Research letters: 500	NA	Maximum of 3 authors and 5 references; must be received within 6 weeks of an article's publication; tables and figures are included selectively
Medical Writings	Expanded reviews of medical and other books and software of contemporary importance to physicians, explorations into the complexities of medical language, and essays on the interface between medicine and literature	2000	None	Essays on general topics of interest to internists are also welcome
Lingua Medica	Commentary and essays on the use and misuse of language in medicine	2000	None	
Medicine and Public Issues	Papers on economic, ethical, sociologic, and political environment in medicine	2500	Unstructured	
On Being a Doctor	Short essays on illuminating experiences in practice	1500	NA	
On Being a Patient	Short essays by physicians on their own experience of illness, accounts written by their patients, or accounts of the experiences of patients' families	1500	NA	Autobiographical writings on illness by published authors are acceptable; fiction is welcome
Personae	Photogarphs that catch people in the context of their lives and that capture personality	NA	NA	Black-and-white photographs of a standard size should be submitted; written permission from the subject(s) is required; photographs cannot be returned
Perspectives	Essays expressing opinions, presenting hypotheses, or considering controversial issues	1500	Unstructured	References are desirable
Position Papers	Summaries of official or consensual positions on issues pertinent to medical practice; includes guidelines.	4000	Unstructured	Procedures used to formulate positions and a bibliography of sources upon which the position is based should be included
Quotations	Should refer, however tangentially, to the practice of medicine	100	NA	A reference to the source of the quotation should be included
Reviews and Updates	Detailed surveys of new scientific developments relevant to medicine; summaries of recent, rapid evolution of development of concepts and practices; summaries of recent key papers described in a standard format	4000	Structured for systematic reviews; unstructured for others	Authors of reviews and updates should state procedures for finding, selecting, and critiquing literature; authors interested in submitting an Update should contact a member of the *Annals* editorial staff for information

*CONSORT = Consolidated Standards of Reporting Trials; MOOSE = Meta-Analysis of Observational Studies in Epidemiology; NA = not applicable.

†Abstracts for articles other than Brief Communications are limited to 250 words; those for Brief Communications, to 150 words.

‡The structure of the abstract for a systematic review or meta-analysis differs from that of other articles (*see* preceding page).

§For more information, see the first page of the Letters section in each issue.


DEFEND THEM AT EVERY MEAL
120 mg
tablet a.c.

STARLIX® (nateglinide) protects against postmeal glucose spikes to significantly improve HbA_{1c}[1,2]

As initial monotherapy

- When diet and exercise fail to control hyperglycemia, and...
- When patients have not been chronically treated with other oral antidiabetic agents

In combination with metformin

Patients who have been chronically treated with a sulfonylurea should not add or be switched to STARLIX.

Excellent safety and tolerability

- Avoids 24-hour stimulation of the pancreas
- Low potential for hypoglycemia
  - — 2.4% incidence, vs 0.4% with placebo
  - — Only 0.3% of patients discontinued STARLIX due to hypoglycemia
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Please see brief summary of complete Prescribing Information on adjacent page.

The most common adverse events associated with STARLIX vs placebo were upper respiratory infection (10.5% vs 8.1%), flu symptoms (3.6% vs 2.6%), dizziness (3.6% vs 2.2%), and arthropathy (3.3% vs 2.2%).

STARLIX®
(nateglinide)
THE MEALTIME GUARDIAN

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Starlix®

(nateglinide)
Tablets

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

Prescribing Information

INDICATIONS AND USAGE

Starlix® (nateglinide) is indicated as monotherapy to lower blood glucose in patients with Type 2 diabetes (non-insulin dependent diabetes mellitus, NIDDM) whose hyperglycemia cannot be adequately controlled by diet and physical exercise and who have not been chronically treated with other anti-diabetic agents.

Starlix is also indicated for use in combination with metformin. In patients whose hyperglycemia is inadequately controlled with metformin, Starlix may be added to, but not substituted for, metformin.

Patients whose hyperglycemia is not adequately controlled with glyburide or other insulin secretagogues should not be switched to Starlix, nor should Starlix be added to their treatment regimen.

CONTRAINDICATIONS

Starlix® (nateglinide) is contraindicated in patients with:
1. Known hypersensitivity to the drug or its inactive ingredients.
2. Type 1 diabetes.
3. Diabetic ketoacidosis. This condition should be treated with insulin.

PRECAUTIONS

Hypoglycemia: All oral blood glucose lowering drugs that are absorbed systemically are capable of producing hypoglycemia. The frequency of hypoglycemia is related to the severity of the diabetes, the level of glycemic control, and other patient characteristics. Geriatric patients, malnourished patients, and those with adrenal or pituitary insufficiency are more susceptible to the glucose lowering effect of these treatments. The risk of hypoglycemia may be increased by strenuous physical exercise, ingestion of alcohol, insufficient caloric intake on an acute or chronic basis, or combinations with other oral antidiabetic agents. Hypoglycemia may be difficult to recognize in patients with autonomic neuropathy and/or those who use beta-blockers. Starlix® (nateglinide) should be administered prior to meals to reduce the risk of hypoglycemia. Patients who skip meals should also skip their scheduled dose of Starlix to reduce the risk of hypoglycemia.

Hepatic Impairment: Starlix should be used with caution in patients with moderate-to-severe liver disease because such patients have not been studied.

Loss of Glycemic Control

Transient loss of glycemic control may occur with fever, infection, trauma, or surgery. Insulin therapy may be needed instead of Starlix therapy at such times. Secondary failure, or reduced effectiveness of Starlix over a period of time, may occur.

Information for Patients

Patients should be informed of the potential risks and benefits of Starlix and of alternative modes of therapy. The risks and management of hypoglycemia should be explained. Patients should be instructed to take Starlix 1 to 30 minutes before ingesting a meal, but to skip their scheduled dose if they skip the meal so that the risk of hypoglycemia will be reduced. Drug interactions should be discussed with patients. Patients should be informed of potential drug-drug interactions with Starlix.

Laboratory Tests

Response to therapies should be periodically assessed with glucose values and HbA_{1C} levels.

Drug Interactions

In vitro drug metabolism studies indicate that Starlix is predominantly metabolized by the cytochrome P450 isozyme CYP2C9 (70%) and to a lesser extent CYP3A4 (30%). Starlix is a potential inhibitor of the CYP2C9 isoenzyme *in vivo* as indicated by its ability to inhibit the *in vitro* metabolism of tolbutamide. Inhibition of CYP3A4 metabolic reactions was not detected in *in vitro* experiments.

Glyburide: In a randomized, multiple-dose crossover study, patients with Type 2 diabetes were administered 120 mg Starlix three times a day before meals for 1 day in combination with glyburide 10 mg daily. There were no clinically relevant alterations in the pharmacokinetics of either agent.

Metformin: When Starlix 120 mg three times daily before meals was administered in combination with metformin 500 mg three times daily to patients with Type 2 diabetes, there were no clinically relevant changes in the pharmacokinetics of either agent.

Digoxin: When Starlix 120 mg before meals was administered in combination with a single 1-mg dose of digoxin to healthy volunteers, there were no clinically relevant changes in the pharmacokinetics of either agent.

Warfarin: When healthy subjects were administered Starlix 120 mg three times daily before meals for four days in combination with a single dose of warfarin 30 mg on day 2, there were no alterations in the pharmacokinetics of either agent. Prothrombin time was not affected.

Diclofenac: Administration of morning and lunch doses of Starlix 120 mg in combination with a single 75-mg dose of diclofenac in healthy volunteers resulted in no significant changes to the pharmacokinetics of either agent.

Nateglinide is highly bound to plasma proteins (98%), mainly albumin. *In vitro* displacement studies with highly protein-bound drugs such as furosemide, propranolol, captopril, nicardipine, pravastatin, glyburide, warfarin, phenytoin, acetylsalicylic acid, tolbutamide, and metformin showed no influence on the extent of nateglinide protein binding. Similarly, nateglinide had no influence on the serum protein binding of propranolol, glyburide, nicardipine, warfarin, phenytoin, acetylsalicylic acid, and tolbutamide *in vitro*. However, prudent evaluation of individual cases is warranted in the clinical setting.

Certain drugs, including nonsteroidal anti-inflammatory agents (NSAIDs), salicylates, monoamine oxidase inhibitors, and non-selective beta-adrenergic-blocking agents may potentiate the hypoglycemic action of Starlix and other oral antidiabetic drugs.

Certain drugs including thiazides, corticosteroids, thyroid products, and sympathomimetics may reduce the hypoglycemic action of Starlix and other oral antidiabetic drugs.

When these drugs are administered to or withdrawn from patients receiving Starlix, the patient should be observed closely for changes in glycemic control.

Drug/Food Interactions

The pharmacokinetics of nateglinide were not affected by the composition of a meal (high protein, fat, or carbohydrate). However, peak plasma levels were significantly reduced when Starlix was administered 10 minutes prior to a liquid meal. Starlix did not have any effect on gastric emptying in healthy subjects as assessed by acetaminophen testing.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Carcinogenicity: A two-year carcinogenicity study in Sprague-Dawley rats was performed with oral doses of nateglinide up to 900 mg/kg/day, which produced AUC exposures in male and female rats approximately 30 and 40 times the human therapeutic exposure respectively with a recommended Starlix dose of 120 mg, three times daily before meals. A two-year carcinogenicity study in B6C3F1 mice was performed with oral doses of nateglinide up to 400 mg/kg/day, which produced AUC exposures in male and female mice approximately 10 and 30 times the human therapeutic exposure with a recommended Starlix dose of 120 mg, three times daily before meals. No evidence of a tumorigenic response was found in either rats or mice.

Mutagenesis: Nateglinide was not genotoxic in the *in vitro* Ames test, mouse lymphoma assay, chromosome aberration assay in Chinese hamster lung cells, or in the *in vivo* mouse micronucleus test.

Impairment of Fertility: Fertility was unaffected by administration of nateglinide to rats at doses up to 600 mg/kg (approximately 16 times the human therapeutic exposure with a recommended Starlix dose of 120 mg three times daily before meals).

Pregnancy

Pregnancy Category C

Nateglinide was not teratogenic in rats at doses up to 1000 mg/kg (approximately 60 times the human therapeutic exposure with a recommended Starlix dose of 120 mg, three times daily before meals). In the rabbit, embryonic development was adversely affected and the incidence of gallbladder agenesis or small gallbladder was increased at a dose of 500 mg/kg (approximately 40 times the human therapeutic exposure with a recommended Starlix dose of 120 mg, three times daily before meals). There are no adequate and well-controlled studies in pregnant women. Starlix should not be used during pregnancy.

Labor and Delivery

The effect of Starlix on labor and delivery in humans is not known.

Nursing Mothers

Studies in lactating rats showed that nateglinide is excreted in the milk; the AUC_{0-48h} ratio in milk to plasma was approximately 1:4. During the peri- and postnatal period body weights were lower in offspring of rats administered nateglinide at 1000 mg/kg (approximately 60 times the human therapeutic exposure with a recommended Starlix dose of 120 mg, three times daily before meals). It is not known whether Starlix is excreted in human milk. Because many drugs are excreted in human milk, Starlix should not be administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Starlix in pediatric patients have not been established.

Geriatric Use

No differences were observed in safety or efficacy of Starlix between patients age 65 and over, and those under age 65. However, greater sensitivity of some older individuals to Starlix therapy cannot be ruled out.

ADVERSE REACTIONS

In clinical trials, approximately 2400 patients with Type 2 diabetes were treated with Starlix® (nateglinide). Of these, approximately 1200 patients were treated for 6 months or longer and approximately 190 patients for one year or longer.

Hypoglycemia was relatively uncommon in all treatment arms of the clinical trials. Only 0.3% of Starlix patients discontinued due to hypoglycemia. Gastrointestinal symptoms, especially diarrhea and nausea, were no more common in patients using the combination of Starlix and metformin than in patients receiving metformin alone. The following table lists events that occurred more frequently in Starlix patients than placebo patients in controlled clinical trials.

Common Adverse Events (≥ 2% in Starlix® patients) in Starlix® Monotherapy Trials (% of patients)

	Placebo *N=458*	**Starlix** *N=1441*
Preferred Term		
Upper Respiratory Infection	8.1	10.5
Back Pain	3.7	4.0
Flu Symptoms	2.6	3.6
Dizziness	2.2	3.6
Arthropathy	2.2	3.3
Diarrhea	3.1	3.2
Accidental Trauma	1.7	2.9
Bronchitis	2.6	2.7
Coughing	2.2	2.4
Hypoglycemia	0.4	2.4

Laboratory Abnormalities

Uric acid: There were increases in mean uric acid levels for patients treated with Starlix alone, Starlix in combination with metformin, metformin alone, and glyburide alone. The respective differences from placebo were 0.29 mg/dL, 0.45 mg/dL, 0.28 mg/dL, and 0.19 mg/dL. The clinical significance of these findings is unknown.

Storage

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

Dispense in a tight container, USP.

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All studies that include numerical data and use statistical inference must include a section under Methods that describes the methods used for the statistical analysis, including the specific statistical software, in detail. If the authors use Bayesian methods as an adjunct to frequentist approaches, they should state the process by which they obtained the prior probabilities. They should include the results from such analyses under Results with the subheading "Bayesian Data Interpretation." This section should also make clear the relative contributions of the prior distribution and the data, through the reporting of the Bayes factors and posterior probabilities for various priors (13). We encourage authors to use graphical presentations of prior distributions, likelihoods, and posterior distributions.

The Editors offer specific advice to authors who are undertaking a review:

Narrative reviews should give the reader a good understanding of a topic. They are appropriate for describing the history or development of a problem and its management. Narrative reviews are especially suitable for describing cutting-edge developments, especially if research is scant or if studies are of relative poor quality. They are useful for discussing data in light of underlying theory and context.

Systematic reviews summarize a body of evidence and draw conclusions that sometimes change practice. They usually focus on one aspect of a topic.

Annals welcomes both forms of review, but the editors advise potential authors to choose the form that suits their purpose. Authors who want to write an article that they hope will change practice should write a systematic review using the following guidelines:

Answer a specific question: Have one or more very well-defined questions that you attempt to answer or address with their review. Typically, the sentence that contains this question would specify the population of interest, the diagnosis of interest, the intervention or cause or prognostic factors of interest, and the outcomes of interest. Having a well-defined question to answer makes it easier to write the review and easier to keep the reader's attention. It also increases the chance that the review will improve practice.

Collaborate: Collaborate with authors who have complementary skills. Authors with well-developed critical appraisal skills help to assure a systematic approach to evaluating the evidence. Authors with clinical expertise in the topic help to focus the review on the right questions and can tell the reader when it seems reasonable to go beyond the evidence and when it might not be reasonable to do so. Having more than one author helps to assure balance and richness and avoid errors in interpretation.

Separate the wheat from the chaff: A review should focus on synthesizing or integrating the body of literature on the question of interest. One of the key tasks for the author is to separate the wheat from the chaff, so that the conclusions reflect the very best evidence. The reviewer should have a systematic way to identify articles that contain the best-quality evidence. The reviewer should try to identify patterns in the literature, pointing out consistencies and inconsistencies, and identifying the best evidence.

Summarize: End the review with clear, crisp summaries of key take-home points and a discussion that focuses on limitations as well implications. The take-home points should link back to the original questions that the review set out to answer. They should be as practical as possible and directed toward clinical readers. Justify a recommendation by showing how the evidence supports it.

Discussion and Conclusions

We suggest structuring the discussion of research findings in the following sequence: 1) A brief synopsis of the key findings, with particular emphasis on how the research findings add to the body of pertinent knowledge. 2) Consideration of possible mechanisms and explanations. 3) Comparison with relevant findings from other published studies (whenever possible, the authors should do a systematic review of all relevant previous studies and combine the results of the submitted study to produce a new estimate of the strength of the evidence [see Statistical Considerations]); 4) Limitations of the present study and methods used to minimize and compensate for those limitations. The paper should conclude with a brief section that summarizes the clinical and research implications of the work, as appropriate.

References

Do 1) Number references in the order in which they first appear in the text. 2) Use Arabic numerals in parentheses. 3) Use the reference style of the National Library of Medicine, including the abbreviations of journal titles. 4) Provide complete data for each reference. 5) Include an "available from" note for documents that may not be readily accessible. 6) Cite symposium papers only from published proceedings. 7) When citing an article or book accepted for publication but not yet published, include the title of the journal (or name of the publisher) and the year of expected publication. 8) Include references to unpublished material in the text, not in the references (for example, papers presented orally at a meeting; unpublished work [personal communications, papers in preparation]), and submit a letter of permission from the cited persons to cite such communications (in general, avoid citations to unpublished scientific results). 9) Ensure that URLs used as references are active and available (the references should include the date on which the author accessed the URL)—for an example, see Citations of Electronic References, below

Do not use ibid. or op cit.

The sample references conform to the style specified by the Uniform Requirements agreement.

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1. **Standard article**

Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med. 1996;124: 980-3.

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Clinical exercise stress testing. Safety and performance guidelines. The Cardiac Society of Australia and New Zealand. Med J Aust. 1996;164: 282-4.

3. **Supplement**

Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect. 1994;102(Suppl 1):275-82.

4. **Special format** (also applies to abstracts and editorials)

Enzensberger W, Fischer PA. Metronome in Parkinson's disease [Letter]. Lancet. 1996;347:1337.

Books: List all authors or editors when there are six or fewer; when there are seven or more authors, list only the first six and add "et al."

1. **Author**

Ringsven MK, Bond D. Gerontology and Leadership Skills for Nurses. 2nd ed. Albany, NY: Delmar; 1996.

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Norman IJ, Redfern SJ, eds. Mental Health Care for Elderly People. New York: Churchill Livingstone; 1996.

3. **Chapter in a book**

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, eds. Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York: Raven Pr; 1995:465-78.

4. **Published proceedings paper**

Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, eds. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 6–10 September 1992; Geneva, Switzerland. Amsterdam: North-Holland; 1992:1561-5.

Other Citations in Reference List

1. **In press** (must have journal title)

Leshner AI. Molecular mechanisms of cocaine addiction. N Engl J Med. 1996; [In press].

2. **Magazine article**

Roberts JL. Villain or victim? Newsweek. 1996;4 Nov:40-1.

In-Text Citations of Unpublished Material (to be placed in parentheses)

1. **Personal communication**

(Strott CA, Nugent CA. Personal communication).

2. **Unpublished papers**

(Lerner RA, Dixon FJ. The induction of acute glomerulonephritis in rats. In preparation)

(Smith J. New agents for cancer chemotherapy. Presented at the Third Annual Meeting of the American Cancer Society, 13 June 1983, New York)

Citations of Electronic References

Cisler S. MediaTracks. Public Access Comput Syst Rev [serial on-line] 1990;109-15. Available from Public Access Computer Systems Forum PACS-L at www.pubaccess.com. Accessed 29 Nov 1997.

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Give the units of measure for all numerical data in a column or row. Place units of measure under a column heading or at the end of a side heading only if those units apply to all numerical data within the column or row.

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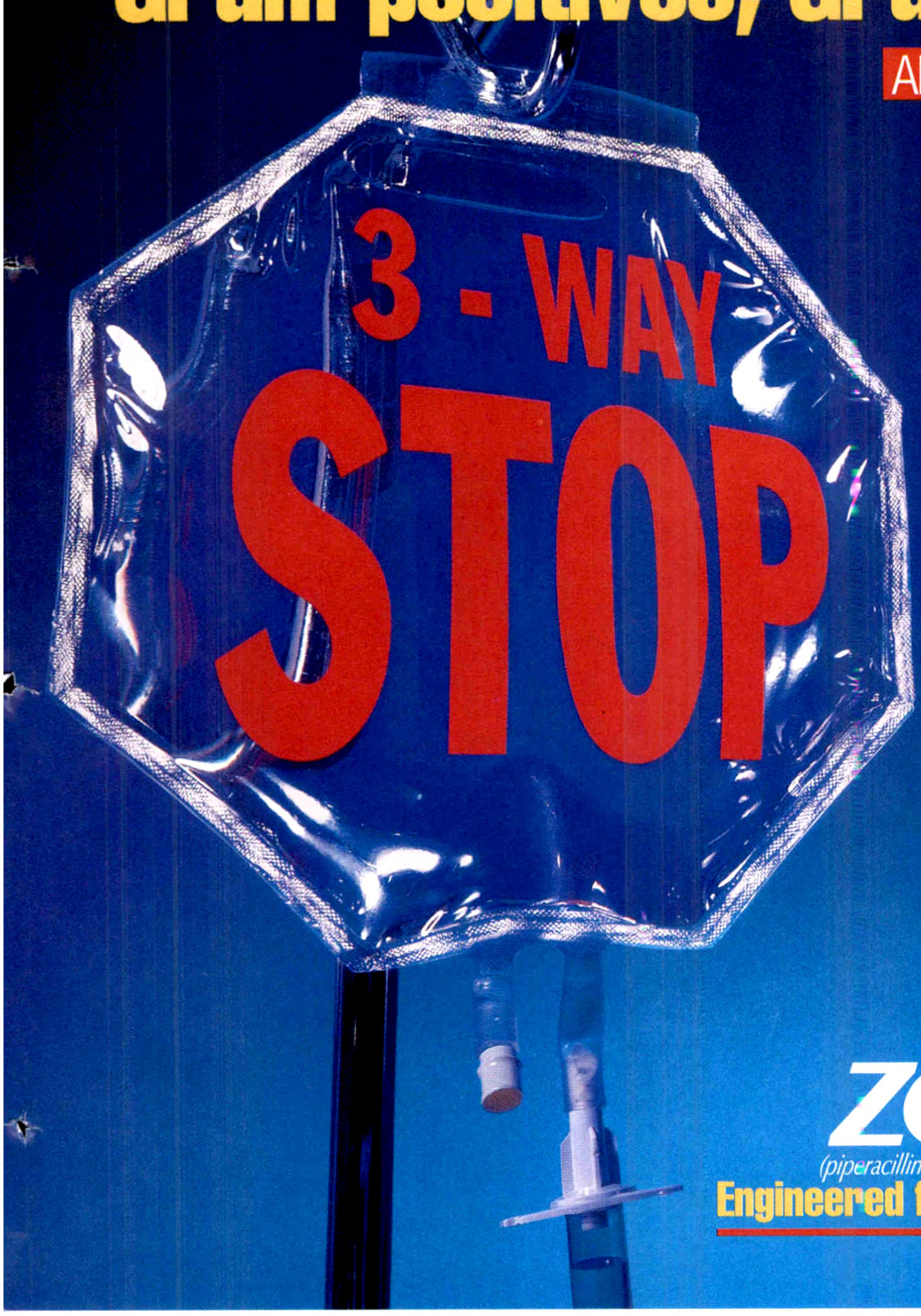
Gram-positives, Gram-negatives AND Anaerobes*‡



- Covers enterococci, *Staphylococcus aureus*,§ *Pseudomonas aeruginosa*, and *Bacteroides fragilis*[1]†‡
- Minimizes *Clostridium difficile* disease (CDD)[2,3]
- Minimizes development of vancomycin-resistant enterococci (VRE)[4]
- ZOSYN is not appropriate therapy for known VRE or CDD

* Indicated for intra-abdominal infections, skin and skin structure infections, community-acquired pneumonia, and nosocomial pneumonia.

† Due to susceptible strains of indicated organisms (see Indications and Usage section of Prescribing Information for a complete listing). Infections caused by piperacillin-susceptible organisms for which piperacillin has been shown to be effective are also amenable to ZOSYN due to its piperacillin content.

ZOSYN IV®
(piperacillin sodium/tazobactam sodium)
Engineered for empiric efficacy

Careful inquiry should be made concerning previous hypersensitivity reaction, as serious and occasionally fatal anaphylactic reactions have been reported in patients receiving therapy with penicillins. ZOSYN is contraindicated in patients with a history of these reactions to any of the penicillins, cephalosporins, or beta-lactamase inhibitors.

The most commonly reported drug-related adverse events in monotherapy clinical trials included diarrhea (11.3%), headache (7.7%), constipation (7.7%), nausea (6.9%), and insomnia (6.6%).

During clinical trials, pseudomembranous colitis has been rarely reported (<1%).

While ZOSYN possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, during prolonged therapy is advisable.

‡ Although a useful guide, *in vitro* activity does not necessarily correlate with specific therapeutic results.

§ Methicillin-susceptible strains.

Please see adjacent brief summary of Prescribing Information.

ZOSYN® (Sterile Piperacillin Sodium and Tazobactam Sodium)
Brief Summary

See package insert for full prescribing information.

INDICATIONS AND USAGE

For the treatment of patients with moderate to severe infections caused by piperacillin-resistant, piperacillin/tazobactam-susceptible, β-lactamase producing strains of the designated microorganisms in the specified conditions listed below:

Appendicitis (complicated by rupture or abscess) and peritonitis caused by *Escherichia coli* or the following members of the *Bacteroides fragilis* group: *B. fragilis, B. ovatus, B. thetaiotaomicron*, or *B. vulgatus*.

Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses, and ischemic/diabetic foot infections caused by *Staphylococcus aureus*.

Postpartum endometritis or pelvic inflammatory disease caused by *Escherichia coli*.

Community-acquired pneumonia (moderate severity only) caused by *Haemophilus influenzae*.

Nosocomial pneumonia (moderate to severe) caused by *Staphylococcus aureus*.

Infections caused by piperacillin-susceptible organisms, for which piperacillin has been shown to be effective, are also amenable to ZOSYN treatment due to its piperacillin content. Treatment of mixed infections caused by piperacillin-susceptible organisms and piperacillin-resistant, β-lactamase producing organisms susceptible to ZOSYN should not require the addition of another antibiotic.

ZOSYN is useful as presumptive therapy in the indicated conditions prior to the identification of causative organisms because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic organisms.

CONTRAINDICATIONS

ZOSYN is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or β-lactamase inhibitors.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ZOSYN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, ZOSYN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ZOSYN, and may range in severity from mild to life-threatening. Consider this diagnosis in patients who present with diarrhea after antibacterial agent administration.

After the diagnosis of pseudomembranous colitis has been established, initiate therapeutic measures. Mild cases usually respond to drug discontinuation alone. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis may be necessary.

PRECAUTIONS

General: Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics, including piperacillin. These reactions have sometimes been associated with coagulation test abnormalities such as clotting time, platelet aggregation, and prothrombin time and are more likely to occur in renal failure patients. If bleeding manifestations occur, discontinue ZOSYN and institute appropriate therapy.

The possibility of the emergence of resistant organisms that might cause superinfections should be kept in mind. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

ZOSYN is a monosodium salt of piperacillin and a monosodium salt of tazobactam, containing 2.35 mEq (54 mg) of $Na+$ per gram of piperacillin; consider this when treating patients requiring restricted salt intake. Perform periodic electrolyte determinations in patients with low potassium reserves; the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

As with other semisynthetic penicillins, piperacillin has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

Laboratory Tests: Perform periodic assessment of hematopoietic function, especially with prolonged therapy, i.e., ≥21 days. (See **ADVERSE REACTIONS—Adverse Laboratory Events.**)

Drug Interactions: *Aminoglycosides*—The mixing of ZOSYN with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside. (See Full Prescribing Information—**Compatible Intravenous Diluent Solutions, DOSAGE AND ADMINISTRATION.**)

When ZOSYN was co-administered with tobramycin, the area under the curve, renal clearance, and urinary recovery of tobramycin were decreased by 11%, 32%, and 38%, respectively. Pharmacokinetic alterations of tobramycin when administered with ZOSYN may be due to *in vivo* and *in vitro* inactivation of tobramycin in the presence of piperacillin/tazobactam. The inactivation of aminoglycosides in the presence of penicillin-class drugs has been recognized. It has been postulated that microbiologically inactive penicillin-aminoglycoside complexes of unknown toxicity form. In patients with severe renal dysfunction (i.e., chronic hemodialysis patients), tobramycin pharmacokinetics are significantly altered when administered with piperacillin. The alteration of tobramycin pharmacokinetics and the potential toxicity of the penicillin-aminoglycoside complexes in patients with mild to moderate renal dysfunction who are administered an aminoglycoside with ZOSYN are unknown.

Probenecid—Probenecid administered with ZOSYN prolongs the half-life of piperacillin by 21% and of tazobactam by 71%.

Vancomycin—No pharmacokinetic interactions with ZOSYN have been noted.

Heparin—Coagulation parameters should be tested more frequently and monitored regularly during simultaneous administration of high doses of heparin, oral anticoagulants, or other drugs that may affect the blood coagulation system or the thrombocyte function.

Vecuronium—Piperacillin used with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. ZOSYN could produce the same phenomenon if given with vecuronium. Due to their similar mechanism of action, the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. (See package insert for vecuronium bromide.)

Drug/Laboratory Test Interactions: As with other penicillins, ZOSYN may result in a false-positive reaction for glucose in the urine using a copper-reduction method (CLINITEST®[§]). Glucose tests based on enzymatic glucose oxidase reactions (such as DIASTIX®[§] or TES-TAPE®[§]) are recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term carcinogenicity studies in animals have not been conducted with piperacillin/tazobactam, piperacillin, or tazobactam. *Piperacillin/tazobactam* was negative in the following mutagenicity tests/assays up to the concentrations noted: microbial mutagenicity assay (14.84/1.86 µg/plate), unscheduled DNA synthesis (UDS) test (5689/711 µg/mL), mammalian point mutation (Chinese hamster ovary cell HPRT) assay (8000/1000 µg/mL), and a mammalian cell (BALB/c-3T3) transformation assay (8/1 µg/mL). *In vivo*, piperacillin/tazobactam did not induce chromosomal aberrations in rats dosed I.V. with 1500/187.5 mg/kg; this dose is similar to the maximum recommended human daily (MRHD) dose on a body-surface-area basis (BSA) (mg/m^2).

Piperacillin was negative in the following mutagenicity tests/assays up to the concentrations noted: microbial mutagenicity assays (50 µg/plate), UDS test (10,000 µg/mL), and a cell (BALB/c-3T3) transformation assay (3000 µg/mL). There was no DNA damage in bacteria (Rec assay) exposed to piperacillin at concentrations up to 200 µg/disk. In a mammalian point mutation (mouse lymphoma cells) assay, piperacillin was positive at concentrations ≥2500 µg/mL. *In vivo*, piperacillin did not induce chromosomal aberrations in mice at I.V. doses up to 2000 mg/kg/day or rats at I.V. doses up to 1500 mg/kg/day. These doses are half (mice) or similar to (rats) the MRHD dose based on BSA (mg/m^2). In another *in vivo* test, there was no dominant lethal effect when piperacillin was administered to rats at I.V. doses up to 2000 mg/kg/day, which is similar to the MRHD dose based on BSA (mg/m^2). When mice were administered piperacillin at I.V. doses up to 2000 mg/kg/day, which is half the MRHD dose based on BSA (mg/m^2), urine from these animals was not mutagenic when tested in a microbial mutagenicity assay. Bacteria injected into the peritoneal cavity of mice administered piperacillin at I.V. doses up to 2000 mg/kg/day did not show increased mutation frequencies.

Tazobactam was negative in the following mutagenicity assays up to the concentrations noted: microbial mutagenicity assays (333 µg/plate), UDS test (2000 µg/mL), mammalian point mutation (Chinese hamster ovary cell HPRT) (5000 µg/mL), a cell (BALB/c-3T3) transformation assay (900 µg/mL). In another mammalian point mutation (mouse lymphoma cells) assay, tazobactam was positive at concentrations ≥3000 µg/mL. In an *in vitro* cytogenetics (Chinese hamster lung cells) assay, tazobactam was negative at concentrations up to 3000 µg/mL. *In vivo*, tazobactam did not induce chromosomal aberrations in rats at I.V. doses up to 5000 mg/kg, which is 23 times the MRHD dose based on BSA (mg/m^2).

Pregnancy: *Teratogenic effects—Pregnancy Category B:* Piperacillin/tazobactam: Reproduction studies in rats have revealed no evidence of impaired fertility due to piperacillin/tazobactam administered up to a dose which is similar to the MRHD dose based on BSA (mg/m^2).

Teratology studies in mice and rats have revealed no evidence of harm to the fetus due to piperacillin/tazobactam administered up to a dose which is 1 to 2 times and 2 to 3 times the human dose of piperacillin and tazobactam, respectively, based on BSA (mg/m^2).

Piperacillin: Reproduction and teratology studies in mice and rats have revealed no evidence of impaired fertility or fetal harm due to piperacillin administered up to a dose which is half (mice) or similar to (rats) the MRHD dose based on BSA (mg/m^2).

Tazobactam: Reproduction studies in rats have revealed no evidence of impaired fertility due to tazobactam administered at doses up to 3 times the MRHD dose based on BSA (mg/m^2).

Teratology studies in mice and rats have revealed no evidence of fetal harm due to tazobactam administered at doses up to 6 and 14 times, respectively, the human dose based on BSA (mg/m^2). In rats, tazobactam crosses the placenta. Concentrations in the fetus are less than or equal to 10% of those found in maternal plasma.

There are no adequate and well-controlled studies with the piperacillin/tazobactam combination or with piperacillin or tazobactam alone in pregnant women. Use this drug during pregnancy only if clearly needed.

Nursing Mothers: Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Exercise caution when ZOSYN is administered to a nursing woman.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Patients over 65 years are **not** at an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency.

ADVERSE REACTIONS

During the initial clinical investigations, 2621 patients worldwide were treated with ZOSYN in phase 3 trials. In the key North American clinical trials (n=830 patients), 90% of the adverse events reported were mild to moderate in severity and transient in nature. However, in 3.2% of the patients treated worldwide, ZOSYN was discontinued because of adverse events primarily involving the skin (1.3%), including rash and pruritus; the gastrointestinal system (0.9%), including diarrhea, nausea, and vomiting; and allergic reactions (0.5%).

Adverse local reactions that were reported, irrespective of relationship to ZOSYN therapy, were phlebitis (1.3%), injection site reaction (0.5%), pain (0.2%), inflammation (0.2%), thrombophlebitis (0.2%), and edema (0.1%).

In the completed study of nosocomial lower respiratory tract infections, 155 patients received ZOSYN 3.375 g every 4 hours in combination with an aminoglycoside. In this trial, 88.5% of the adverse experiences reported were mild to moderate in severity and transient in nature. In this trial, ZOSYN was discontinued in four patients (2.6%) due to adverse experiences: thrombocytopenia and pancreatitis in one patient; fever in one patient; fever and eosinophilia in another patient; and diarrhea and elevated liver enzymes in the fourth patient.

Adverse Clinical Events: Based on patients from the North American trials (n=1063), the events with the highest incidence in patients, irrespective of relationship to ZOSYN therapy, were diarrhea (11.3%); headache (7.7%); constipation (7.7%); nausea (6.9%); insomnia (6.6%); rash (4.2%), including maculopapular, bullous, urticarial, and eczematoid; vomiting (3.3%); dyspepsia (3.3%); pruritus (3.1%); stool changes (2.4%); fever (2.4%); agitation (2.1%); pain (1.7%); moniliasis (1.6%); hypertension (1.6%); dizziness (1.4%); abdominal pain (1.3%); chest pain (1.3%); edema (1.2%); anxiety (1.2%); rhinitis (1.2%); and dyspnea (1.1%).

Based on patients in the completed study of nosocomial lower respiratory tract infections (n=155), using every-4-hour dosing and aminoglycoside therapy, the events with the highest incidence in patients, irrespective of relationship to ZOSYN and aminoglycoside therapy, were diarrhea (20%); constipation (8.4%); agitation (7.1%); nausea (5.8%); headache (4.5%); insomnia (4.5%); oral thrush (3.9%); erythematous rash (3.9%); anxiety (3.2%); fever (3.2%); pain (3.2%); pruritus (3.2%); hiccough (2.6%); vomiting (2.6%); dyspepsia (1.9%); edema (1.9%); fluid overload (1.9%); stool changes (1.9%); anorexia (1.3%); cardiac arrest (1.3%); confusion (1.3%); diaphoresis (1.3%); duodenal ulcer (1.3%); flatulence (1.3%); hypertension (1.3%); hypotension (1.3%); inflammation at injection site (1.3%); pleural effusion (1.3%); pneumothorax (1.3%); rash, not otherwise specified (1.3%); supraventricular tachycardia (1.3%); thrombophlebitis (1.3%); and urinary incontinence (1.3%).

Additional adverse systemic clinical events reported in 1.0% or less of the patients in the initial North American trials and/or in the patients administered ZOSYN 3.375 g every 4 hours plus an aminoglycoside in the nosocomial lower respiratory tract study are listed below within each body system (bracketed events occurred only in the nosocomial pneumonia trial): *Autonomic nervous system:* hypotension, ileus, syncope. *Body as a whole:* rigors, back pain, malaise, [asthenia, chest pain]. *Cardiovascular:* tachycardia, including supraventricular and ventricular; bradycardia; arrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction, [angina]. *Central nervous system:* tremor, convulsions, vertigo, [aggressive reaction (combative)]. *Gastrointestinal:* melena, flatulence, hemorrhage, gastritis, hiccough, ulcerative stomatitis, [fecal incontinence, gastric ulcer, pancreatitis]. Pseudomembranous colitis was reported in one patient during the clinical trials. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS**.) *Hearing and vestibular system:* tinnitus, [deafness, earache]. *Hypersensitivity:* anaphylaxis. *Metabolic and Nutritional:* symptomatic hypoglycemia, thirst, [gout, vitamin B_{12} deficiency anemia]. *Musculoskeletal:* myalgia, arthralgia. *Platelets, Bleeding, Clotting:* mesenteric embolism, purpura, epistaxis, pulmonary embolism, [ecchymosis, hemoptysis] (See **PRECAUTIONS—General**). *Psychiatric:* confusion, hallucination, depression. *Reproductive, Female:* leukorrhea, vaginitis, [perineal irritation/pain]. *Reproductive, Male:* [balanoposthitis]. *Respiratory:* pharyngitis, pulmonary edema, bronchospasm, coughing, [atelectasis, dyspnea, hypoxia]. *Skin and Appendages:* genital pruritus, diaphoresis, [conjunctivitis, xerosis]. *Special senses:* taste perversion. *Urinary:* retention, dysuria, oliguria, hematuria, incontinence, [urinary tract infection with trichomonas, yeast in urine]. *Vision:* photophobia. *Vascular (extracardiac):* flushing, [cerebrovascular accident].

Additional adverse events reported from worldwide marketing experience with ZOSYN, where causal relationship to ZOSYN is uncertain: *Gastrointestinal:* hepatitis, cholestatic jaundice. *Hematologic:* hemolytic anemia. *Renal:* rarely, interstitial nephritis. *Skin and Appendages:* erythema multiforme and Stevens-Johnson syndrome, rarely reported.

Adverse Laboratory Events (Seen During Clinical Trials): Of the studies reported, including that of nosocomial lower respiratory tract infections in which a higher dose of ZOSYN was used in combination with an aminoglycoside, changes in laboratory parameters, without regard to drug relationship, include: *Hematologic:* decreases in hemoglobin and hematocrit, thrombocytopenia, increases in platelet count, eosinophilia, leukopenia, neutropenia. The leukopenia/neutropenia appears to be reversible and most frequently associated with prolonged administration, i.e., ≥21 days of therapy. These patients were withdrawn from therapy; some had accompanying systemic symptoms (e.g., fever, rigors, chills). *Coagulation:* positive direct Coombs' test, prolonged prothrombin time, prolonged partial thromboplastin time. *Hepatic:* transient elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin. *Renal:* increases in serum creatinine, blood urea nitrogen. *Urinalysis:* proteinuria, hematuria, pyuria.

Additional laboratory events include abnormalities in electrolytes (i.e., increases and decreases in sodium, potassium, and calcium), hyperglycemia, decreases in total protein or albumin.

The following adverse reaction has also been reported for PIPRACIL® (sterile piperacillin sodium): *Skeletal:* prolonged muscle relaxation (See **PRECAUTIONS—Drug Interactions**.)

OVERDOSAGE

Information on overdosage of ZOSYN in humans is not available.

Excessive serum levels of either piperacillin or tazobactam may be reduced by hemodialysis. No specific antidote is known. As with other penicillins, neuromuscular excitability or convulsions have occurred following large intravenous doses, primarily in patients with impaired renal function.

In the case of motor excitability or convulsions, general supportive measures, including administration of anticonvulsive agents (e.g., diazepam or barbiturates) may be considered.

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This Brief Summary is based on ZOSYN direction circulars CI 4630-2 and CI 4813-1 (Revised March 25, 1999).

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Carolina, Puerto Rico 00987

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Annals of Internal Medicine | SUMMARIES FOR PATIENTS

Prednisone for Rheumatoid Arthritis

Summaries for Patients are a service provided by *Annals* to help patients better understand the complicated and often mystifying language of modern medicine.

The full report is titled "Low-Dose Prednisone Therapy for Patients with Early Active Rheumatoid Arthritis: Clinical Efficacy, Disease-Modifying Properties, and Side Effects. A Randomized, Double-Blind, Placebo-Controlled Clinical Trial." It is in the 1 January 2002 issue of *Annals of Internal Medicine* (volume 136, pages 1-12). The authors are AA van Everdingen, JWG Jacobs, DR Siewertsz van Reesema, and JWJ Bijlsma.

What is the problem and what is known about it so far?

Rheumatoid arthritis (RA) is a chronic disease that causes painful, swollen, and deformed joints. It is caused by inflammation of the tissue linings (membranes) of joints and most often affects many small joints of the hands and feet, but may develop in any joint. People with RA usually have chronic joint pain and stiffness. There is no cure for RA, but signs and symptoms can be treated. Persistent arthritis is painful and destroys joints, and about 1 in 10 persons with RA may eventually become severely disabled from joint destruction. Several powerful drugs, named disease-modifying antirheumatic drugs (DMARDs), reduce both symptoms and the risk for permanent joint damage. Other drugs, known as glucocorticoids (prednisone), reduce inflammation and improve symptoms. Recent studies suggest that prednisone also can help prevent joint damage in patients who are taking DMARDs. Whether prednisone prevents joint damage in patients who do not use DMARDs is unclear.

Why did the researchers do this particular study?

To see whether low doses of prednisone prevent joint damage in adults who have early active RA but have little joint damage and use no DMARDs.

Who was studied?

81 adults who had had RA for less than 1 year. None had been treated with DMARDs. Most (64%) were women, and the average age was about 60 years.

How was the study done?

Patients were randomly assigned to receive prednisone (10 mg daily) or placebo (dummy pill) for 2 years. Neither the patients nor their physicians were told who got prednisone or dummy pills. To measure the effect of treatment, the authors assessed joint symptoms and x-rayed the joints every 6 months.

What did the researchers find?

At 6 months, patients who took prednisone had fewer symptoms (joint stiffness, swelling, and tenderness) and better grip strength. During the study, they also used fewer additional therapies (for example, nonsteroidal anti-inflammatory drugs) than patients given dummy pills. One and 2 years after starting treatment, x-rays showed less joint damage with prednisone than with dummy pills. Five patients given prednisone and 2 patients given placebo developed fractures in the small bones of their backs.

What were the limitations of the study?

This study was started almost 10 years ago, before doctors routinely used DMARDs for all patients with RA. Also, patients in this study received only calcium to prevent thinning of their bones and fractures. Using newer therapies in addition to calcium might prevent fractures related to prednisone. Finally, the authors did not test the effect of even lower doses of prednisone, such as 2.5 or 5 mg daily.

What are the implications of the study?

Prednisone in dosages of 10 mg daily improves symptoms in patients with early active RA and prevents progression of joint damage, but it also increases risk for bone fractures.

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The only ß-blocker indicated for hypertension, angina, and heart failure

TOPROL-XL is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, and sick sinus syndrome (unless a permanent pacemaker is in place).

Patients taking TOPROL-XL should avoid abrupt cessation of therapy. Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. The dosage should be reduced gradually over a 1- to 2-week period, and the patient should be carefully monitored. Please see brief summary of full Prescribing Information, including boxed WARNING, on adjacent page.

Low-dose, scored, 25-mg tablet for heart failure

- TOPROL-XL is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents
- TOPROL-XL is indicated in the long-term treatment of angina pectoris
- TOPROL-XL is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis
- The recommended starting dose of TOPROL-XL is 25 mg once daily for 2 weeks in patients with NYHA Class II heart failure and 12.5 mg once daily in patients with more severe heart failure. The dose should then be doubled every 2 weeks to the highest dosage level tolerated or up to a maximum dose of 200 mg
- Worsening cardiac failure may occur during uptitration of TOPROL-XL. (See DOSAGE AND ADMINISTRATION in brief summary of full Prescribing Information.) Patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath

Consistent 24-hour β_1-blockade

Once-a-day
TOPROL-XL®
(metoprolol succinate)
extended-release tablets
25 mg
50 mg
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200 mg

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(metoprolol succinate)

EXTENDED-RELEASE TABLETS

TABLETS: 25 MG, 50 MG, 100 MG, AND 200 MG

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INDICATIONS AND USAGE Hypertension: Toprol-XL is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. **Angina Pectoris:** Toprol-XL is indicated in the long-term treatment of angina pectoris. **Heart Failure:** Toprol-XL is indicated for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. It was studied in patients already receiving ACE inhibitors, diuretics, and, in the majority of cases, digitalis. In this population, Toprol-XL decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure.

CONTRAINDICATIONS Toprol-XL is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, and sick sinus syndrome (unless a permanent pacemaker is in place) (see WARNINGS).

WARNINGS

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Toprol-XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1–2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Toprol-XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Toprol-XL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta$_1$-selectivity, however, Toprol-XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$-selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Toprol-XL should be used (see DOSAGE AND ADMINISTRATION). ***Major Surgery:*** The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures. Toprol-XL, like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers. ***Diabetes and Hypoglycemia:*** Toprol-XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. ***Thyrotoxicosis:*** Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

PRECAUTIONS General: Toprol-XL should be used with caution in patients with impaired hepatic function. Worsening cardiac failure may occur during up-titration of Toprol-XL. If such symptoms occur, diuretics should be increased and the dose of Toprol-XL should not be advanced until clinical stability is restored (see DOSAGE AND ADMINISTRATION). It may be necessary to lower the dose of Toprol-XL or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of Toprol-XL. **Information for Patients:** Patients should be advised to take Toprol-XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not interrupt or discontinue Toprol-XL without consulting the physician. Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Toprol-XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Toprol-XL. Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath. **Laboratory Tests:** Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase. **Drug Interactions:** Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Toprol-XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension. Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate release metoprolol 200 mg, tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor. All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a *Salmonella*/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a *Salmonella*/mammalian-microsome mutagenicity test) were negative. No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. **Pregnancy Category C:** Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers:** Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Toprol-XL is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Clinical studies of Toprol-XL in hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience in hypertensive patients has not identified differences in responses between elderly and younger patients. Of the 1,990 patients with heart failure randomized to Toprol-XL in the MERIT-HF trial, 50% (990) were 65 years of age and older and 12% (238) were 75 years of age and older. There were no notable differences in efficacy or the rate of adverse events between older and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Risk of Anaphylactic Reactions:** While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Once-a-day

TOPROL-XL®

(metoprolol succinate)

extended-release tablets

25 mg
50 mg
100 mg
200 mg

ADVERSE REACTIONS Hypertension and Angina: Most adverse effects have been mild and transient. The following adverse reactions have been reported for metoprolol tartrate. ***Central Nervous System:*** Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported. ***Cardiovascular:*** Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS). ***Respiratory:*** Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS). ***Gastrointestinal:*** Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, and heartburn have been reported in about 1 of 100 patients. ***Hypersensitive Reactions:*** Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported. ***Miscellaneous:*** Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido and tinnitus have also been reported. There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol. **Potential Adverse Reactions:** A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Toprol-XL. ***Central Nervous System:*** Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. ***Cardiovascular:*** Intensification of AV block (see CONTRAINDICATIONS). ***Hematologic:*** Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. ***Hypersensitive Reactions:*** Fever combined with aching and sore throat, laryngospasm, and respiratory distress. **Heart Failure:** In the MERIT-HF study, serious adverse events and adverse events leading to discontinuation of study medication were systematically collected. In the MERIT-HF study comparing Toprol-XL in daily doses up to 200 mg (mean dose 159 mg once-daily) (n=1990) to placebo (n=2001), 10.3% of Toprol-XL patients discontinued for adverse events vs. 12.2% of placebo patients. The table below lists adverse events in the MERIT-HF study that occurred at an incidence of equal to or greater than 1% in the Toprol-XL group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

Adverse Events Occurring in the MERIT-HF Study at an Incidence ≥ 1% in the Toprol-XL Group and Greater Than Placebo by More Than 0.5%

	Toprol-XL N=1990 % of patients	Placebo N=2001 % of patients
Dizziness/vertigo	1.8	1.0
Bradycardia	1.5	0.4
Accident and/or injury	1.4	0.8

Other adverse events with an incidence of > 1% on Toprol-XL and as common on placebo (within 0.5%) included myocardial infarction, pneumonia, cerebrovascular disorder, chest pain, dyspnea/dyspnea aggravated, syncope, coronary artery disorder, ventricular tachycardia/arrhythmia aggravated, hypotension, diabetes mellitus/diabetes mellitus aggravated, abdominal pain, and fatigue. **Post-Marketing Experience:** The following adverse reactions have been reported in post-marketing use: *Gastrointestinal:* hepatitis; *Musculoskeletal:* arthralgia.

OVERDOSAGE Acute Toxicity: There have been a few reports of overdosage with Toprol-XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since Toprol-XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to Toprol-XL. **Signs and Symptoms:** Overdosage of Toprol-XL may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness/coma, nausea, vomiting, and cyanosis. **Treatment:** In general, patients with acute or recent myocardial infarction or congestive heart failure may be more hemodynamically unstable than other patients and should be treated accordingly. When possible the patient should be treated under intensive care conditions. On the basis of the pharmacologic actions of metoprolol, the following general measures should be employed: ***Elimination of the Drug:*** Gastric lavage should be performed. ***Bradycardia:*** Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously. ***Hypotension:*** A vasopressor should be administered, e.g., levarterenol or dopamine. ***Bronchospasm:*** A beta$_2$-stimulating agent and/or a theophylline derivative should be administered. ***Cardiac Failure:*** A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol or glucagon may be considered.

DOSAGE AND ADMINISTRATION Toprol-XL is an extended release tablet intended for once-a-day administration. When switching from immediate release metoprolol tablet to Toprol-XL, the same total daily dose of Toprol-XL should be used. As with immediate release metoprolol, dosages of Toprol-XL should be individualized and titration may be needed in some patients. Toprol-XL tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed. **Hypertension:** The usual initial dosage is 50 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied. **Angina Pectoris:** The dosage of Toprol-XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1–2 weeks (see WARNINGS). **Heart Failure:** Dosage must be individualized and closely monitored during up-titration. Prior to initiation of Toprol-XL, the dosing of diuretics, ACE inhibitors, and digitalis (if used) should be stabilized. The recommended starting dose of Toprol-XL is 25 mg once daily for two weeks in patients with NYHA class II heart failure and 12.5 mg once daily in patients with more severe heart failure. The dose should then be doubled every two weeks to the highest dosage level tolerated by the patient or up to 200 mg of Toprol-XL. If transient worsening of heart failure occurs, it may be treated with increased doses of diuretics, and it may also be necessary to lower the dose of Toprol-XL or temporarily discontinue it. The dose of Toprol-XL should not be increased until symptoms of worsening heart failure have been stabilized. Initial difficulty with titration should not preclude later attempts to introduce Toprol-XL. If heart failure patients experience symptomatic bradycardia, the dose of Toprol-XL should be reduced.

HOW SUPPLIED Tablets containing metoprolol succinate equivalent to the indicated weight of metoprolol tartrate, USP, are white, biconvex, film-coated, and scored.

Tablet	Shape	Engraving	Bottle of 100 NDC 0186-	Unit Dose Packages of 100 NDC 0186-
25 mg*	Oval	A β	1088-05	1088-39
50 mg	Round	A mo	1090-05	1090-39
100 mg	Round	A ms	1092-05	1092-39
200 mg	Oval	A my	1094-05	N/A

*The 25 mg tablet is scored on both sides.

Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F). (See USP Controlled Room Temperature.)

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Manufactured for: AstraZeneca LP
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S-151 85 Södertälje, Sweden

Made in Sweden

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Rev. 10/01

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A potent insulin sensitizer

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Durable glycemic control

- As initial therapy
- In combination with metformin† or sulfonylureas‡1

#1 prescribed TZD*

- Experience you can count on
- Over 12.5 million Rxs with over 2.5 million patients*
- Over 2 years on the market*

* Based on overall physician population, Scott-Levin SPA, August 2001; NDC, August 2001, plus nonretail.

† Patients who received *Avandia* 8 mg qd or *Avandia* 4 mg bid plus 2.5 g/day of metformin for at least 24 months during 2 double-blind, placebo-controlled studies and their 1 open-label extension.

‡ Patients who received *Avandia* 2 mg bid plus glyburide for at least 24 months during a double-blind, 26-week study and its open-label extension.

Reference:
1. Data on file, GlaxoSmithKline.

Please see brief summary of prescribing information on the last page of this advertisement.

Other considerations: *Hypoglycemia*—Patients receiving *Avandia* in combination with other hypoglycemic agents may be at risk for hypoglycemia and a reduction in the dose of the concomitant agent may be necessary. *Edema*—*Avandia* should be used with caution in patients with edema. *Weight gain*—Dose-related weight gain was seen with *Avandia*. *Anemia*—In clinical trials, the frequency of anemia was greater with the combination of *Avandia* plus metformin compared to metformin alone. Lower pretreatment hemoglobin/hematocrit levels may have contributed to this higher reporting rate.

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Insulin-sensitizing
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AVANDIA® (rosiglitazone maleate) tablets

Before prescribing, see complete prescribing information. The following is a brief summary.

INDICATIONS AND USAGE: *Avandia* is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. *Avandia* is indicated as monotherapy. *Avandia* is also indicated for use in combination with a sulfonylurea or metformin when diet, exercise, and a single agent do not result in adequate glycemic control. For patients inadequately controlled with a maximum dose of a sulfonylurea or metformin, *Avandia* should be added to, rather than substituted for, a sulfonylurea or metformin. Prior to initiation of therapy with *Avandia*, investigate and treat secondary causes of poor glycemic control, e.g., infection.

CONTRAINDICATIONS: *Avandia* is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS: Cardiac Failure and Other Cardiac Effects: *Avandia*, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. *Avandia* should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status were not studied during the clinical trials. *Avandia* is not recommended in patients with NYHA Class 3 and 4 cardiac status. In two 26-week U.S. trials involving 611 patients with type 2 diabetes, *Avandia* plus insulin therapy was compared with insulin therapy alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy (34%), retinopathy (19%), ischemic heart disease (14%), vascular disease (9%), and congestive heart failure (2.5%). In these clinical studies an increased incidence of cardiac failure and other cardiovascular adverse events were seen in patients on *Avandia* and insulin combination therapy compared to insulin and placebo. Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were mostly on the higher 8 mg daily dose of *Avandia*. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure on combination therapy. Three of 10 patients who developed cardiac failure on combination therapy during the double blind part of the studies had no known prior evidence of congestive heart failure, or pre-existing cardiac condition. **The use of *Avandia* in combination therapy with insulin is not indicated (see ADVERSE REACTIONS).**

PRECAUTIONS: General: Due to its mechanism of action, *Avandia* is active only in the presence of endogenous insulin. Therefore, *Avandia* should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. ***Hypoglycemia:*** Patients receiving *Avandia* in combination with other hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary. ***Edema:*** *Avandia* should be used with caution in patients with edema. In a clinical study in healthy volunteers who received *Avandia* 8 mg once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo. Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, *Avandia* should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see WARNINGS, Cardiac Failure and Other Cardiac Effects and PRECAUTIONS, Information for Patients). In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with *Avandia*, and may be dose related. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and *Avandia* (see ADVERSE REACTIONS).

Weight Gain: Dose-related weight gain was seen with *Avandia* alone and in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 1. Weight Changes (kg) from Baseline During Clinical Trials with *Avandia*

		Control Group		***Avandia* 4 mg**	***Avandia* 8 mg**
Monotherapy	**Duration**		**Median (25th, 75th percentile)**	**Median (25th, 75th percentile)**	**Median (25th, 75th percentile)**
	26 weeks	placebo	-0.9 (-2.8, 0.9)	1.0 (-0.9, 3.6)	3.1 (1.1, 5.8)
	52 weeks	sulfonylurea	2.0 (0, 4.0)	2.0 (-0.6, 4.0)	2.6 (0, 5.3)
Combination therapy					
sulfonylurea	26 weeks	sulfonylurea	0 (-1.3, 1.2)	1.8 (0, 3.1)	—
metformin	26 weeks	metformin	-1.4 (-3.2, 0.2)	0.8 (-1.0, 2.6)	2.1 (0, 4.3)
insulin	26 weeks	insulin	0.9 (-0.5, 2.7)	4.1 (1.4, 6.3)	5.4 (3.4, 7.3)

Hematologic: Across all controlled clinical studies, decreases in hemoglobin and hematocrit (mean decreases in individual studies ≤1.0 gram/dL and ≤3.3%, respectively) were observed for *Avandia* alone and in combination with other hypoglycemic agents. The changes occurred primarily during the first 3 months following initiation of *Avandia* therapy or following an increase in *Avandia* dose. White blood cell counts also decreased slightly in patients treated with *Avandia*. The observed changes may be related to the increased plasma volume observed with treatment with *Avandia* and may be dose related (see ADVERSE REACTIONS, Laboratory Abnormalities).

Ovulation: Therapy with *Avandia*, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking *Avandia* (see PRECAUTIONS, Pregnancy, Pregnancy Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known. Although hormonal imbalance has been seen in preclinical studies (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with *Avandia* should be reviewed.

Hepatic Effects: Another drug of the thiazolidinedione class, troglitazone, was associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death were reported during clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT >3X upper limit of normal) compared to placebo. Very rare cases of reversible jaundice were also reported. In pre-approval clinical studies in 4598 patients treated with *Avandia*, encompassing approximately 3600 patient years of exposure, there was no signal of drug-induced hepatotoxicity or elevation of ALT levels. In pre-approval controlled trials, 0.2% of patients treated with *Avandia* had elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with *Avandia* were reversible and were not clearly causally related to therapy with *Avandia*. In postmarketing experience with *Avandia*, reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Rosiglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death during clinical use. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with *Avandia* undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy with *Avandia* in all patients. Therapy with *Avandia* should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). In patients with normal baseline liver enzymes, following initiation of therapy with *Avandia*, it is recommended that liver enzymes be monitored every 2 months for the first 12 months, and periodically thereafter. Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with *Avandia* should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with *Avandia* in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X upper limit of normal in patients on therapy with *Avandia*, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with *Avandia* should be discontinued. There are no data available from clinical trials to evaluate the safety of *Avandia* in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. *Avandia* should not be used in patients who experienced jaundice while taking troglitazone. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with *Avandia* should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Laboratory Tests: Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response. Liver enzyme monitoring is recommended prior to initiation of therapy with *Avandia* in all patients and periodically thereafter (see PRECAUTIONS, *Hepatic Effects* and ADVERSE REACTIONS, Serum Transaminase Levels).

Information for Patients: Patients should be informed of the following. It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. Patients should be advised that it can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see full effect. Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and every 2 months for the first 12 months, and periodically thereafter. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on *Avandia* should immediately report these symptoms to their physician.

Drug Interactions: Drugs Metabolized by Cytochrome P_{450}: *Avandia* was shown to have no clinically relevant drug interactions with nifedipine and oral contraceptives, which are predominantly metabolized by CYP3A4; glyburide, metformin, acarbose, digoxin, warfarin, ethanol and ranitidine. See full prescribing information.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the *in vitro* bacterial assays for gene mutation, the *in vitro* chromosome aberration test in human lymphocytes, the *in vivo* mouse micronucleus test, and the *in vivo/in vitro* rat UDS assay. There was a small (about 2-fold) increase in mutation in the *in vitro* mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Animal Toxicology: Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Morphometric measurement indicated that there was hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

Pregnancy: Pregnancy Category C. There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. *Avandia* should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Labor and Delivery: The effect of rosiglitazone on labor and delivery in humans is not known. **Nursing Mothers:** Drug-related material was detected in milk from lactating rats. It is not known whether *Avandia* is excreted in human milk. Because many drugs are excreted in human milk, *Avandia* should not be administered to a nursing woman.

ADVERSE REACTIONS: In clinical trials, approximately 4600 patients with type 2 diabetes have been treated with *Avandia*; 3300 patients were treated for 6 months or longer and 2000 patients were treated for 12 months or longer. The following adverse events (occurring at rates ≥5% in any treatment group) were reported by patients in double-blind clinical trials with *Avandia* as monotherapy (N=2526), compared to events seen in patients treated with placebo (N=601), metformin (N=225) or sulfonylureas (N=626), respectively: Upper respiratory tract infection (9.9%, 8.7%, 8.9%, 7.3%); injury (7.6%, 4.3%, 7.6%, 6.1%); headache (5.9%, 5.0%, 8.9%, 5.4%); back pain (4.0%, 3.8%, 4.0%, 5.0%); hyperglycemia (3.9%, 5.7%, 4.4%, 8.1%); fatigue (3.6%, 5.0%, 4.0%, 1.9%); sinusitis (3.2%, 4.5%, 5.3%, 3.0%); diarrhea (2.3%, 3.3%, 15.6%, 3.0%), and hypoglycemia (0.6%, 0.2%, 1.3%, 5.9%). The sulfonylurea group includes patients receiving glyburide (N=514), gliclazide (N=91) or glipizide (N=21).

A small number of patients treated with *Avandia* had adverse events of anemia and edema. Overall, these events were generally mild to moderate in severity and usually did not require discontinuation of treatment with *Avandia*. In double-blind studies, anemia was reported in 1.9% of patients receiving *Avandia* compared to 0.7% on placebo, 0.6% on sulfonylureas and 2.2% on metformin. Edema was reported in 4.8% of patients receiving *Avandia* compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. Overall, the types of adverse experiences reported when *Avandia* was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with *Avandia*. Reports of anemia (7.1%) were greater in patients treated with a combination of *Avandia* and metformin compared to monotherapy with *Avandia* or in combination with a sulfonylurea. Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies (see ADVERSE REACTIONS, Laboratory Abnormalities, Hematologic). In 26-week double-blind studies, edema was reported with higher frequency in the *Avandia* plus insulin combination trials (insulin, 5.4%; and *Avandia* in combination with insulin, 14.7%). Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with *Avandia* (see WARNINGS, Cardiac Failure and Other Cardiac Effects). In postmarketing experience with *Avandia*, adverse events potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported.

Laboratory Abnormalities: Hematologic: Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in patients treated with *Avandia* (mean decreases in individual studies up to 1.0 gram/dL hemoglobin and up to 3.3% hematocrit). The time course and magnitude of decreases were similar in patients treated with a combination of *Avandia* and other hypoglycemic agents or *Avandia* monotherapy. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination studies and may have contributed to the higher reporting rate of anemia. White blood cell counts also decreased slightly in patients treated with *Avandia*. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with *Avandia*. **Lipids:** Changes in serum lipids have been observed following treatment with *Avandia* (see CLINICAL STUDIES in the full prescribing information).

Serum Transaminase Levels: In clinical studies in 4598 patients treated with *Avandia* encompassing approximately 3600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels. In controlled trials, 0.2% of patients treated with *Avandia* had reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. Hyperbilirubinemia was found in 0.3% of patients treated with *Avandia* compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In the clinical program including long-term, open-label experience, the rate per 100 patient years exposure of ALT increase to >3X the upper limit of normal was 0.35 for patients treated with *Avandia*, 0.59 for placebo-treated patients, and 0.78 for patients treated with active comparator agents. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. In postmarketing experience with *Avandia*, reports of hepatic enzyme elevations three or more times the upper limit of normal and hepatitis have been received (see PRECAUTIONS, *Hepatic Effects*).

DOSAGE AND ADMINISTRATION: The management of antidiabetic therapy should be individualized. *Avandia* may be administered either at a starting dose of 4 mg as a single daily dose or divided and administered in the morning and evening. For patients who respond inadequately following 8 to 12 weeks of treatment, as determined by reduction in FPG, the dose may be increased to 8 mg daily as indicated below. Reductions in glycemic parameters by dose and regimen are described under CLINICAL STUDIES in the full prescribing information. *Avandia* may be taken with or without food. **Monotherapy:** The usual starting dose of *Avandia* is 4 mg administered either as a single dose once daily or in divided doses twice daily. In clinical trials, the 4 mg twice daily regimen resulted in the greatest reduction in FPG and HbA1c. **Combination Therapy with a Sulfonylurea or Metformin:** When *Avandia* is added to existing therapy, the current dose of sulfonylurea or metformin can be continued upon initiation of *Avandia* therapy. ***Sulfonylurea:*** When used in combination with sulfonylurea, the recommended dose of *Avandia* is 4 mg administered as either a single dose once daily or in divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased. ***Metformin:*** The usual starting dose of *Avandia* in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with *Avandia*. **Maximum Recommended Dose:** The dose of *Avandia* should not exceed 8 mg daily, as a single dose or divided twice daily. The 8 mg daily dose has been shown to be safe and effective in clinical studies as monotherapy and in combination with metformin. Doses of *Avandia* greater than 4 mg daily in combination with a sulfonylurea have not been studied in adequate and well-controlled clinical trials. *Avandia* may be taken with or without food. No dosage adjustments are required for the elderly. No dosage adjustment is necessary when *Avandia* is used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and *Avandia* is also contraindicated in patients with renal impairment. Therapy with *Avandia* should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy) (see PRECAUTIONS, *Hepatic Effects* and CLINICAL PHARMACOLOGY, Hepatic Impairment in full prescribing information). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with *Avandia* and periodically thereafter (see PRECAUTIONS, *Hepatic Effects*). There are no data on the use of *Avandia* in patients under 18 years of age; therefore, use of *Avandia* in pediatric patients is not recommended.

BRS-AV:L6

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*Based on overall physician population, Scott-Levin SPA, August 2001; NDC, August 2001, plus nonretail.

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Avandia, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. *Avandia* should be discontinued if any deterioration in cardiac status occurs.

Hepatic considerations: Liver enzyme monitoring is recommended prior to initiation of *Avandia*, every 2 months for the first 12 months, and periodically thereafter. *Avandia* should not be initiated in patients with clinical evidence of active liver disease or ALT >2.5X the upper limit of normal.

Reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal have been received in postmarketing experience. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

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Annals of Internal Medicine | ARTICLE

Low-Dose Prednisone Therapy for Patients with Early Active Rheumatoid Arthritis: Clinical Efficacy, Disease-Modifying Properties, and Side Effects

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Amalia A. van Everdingen, MD; Johannes W.G. Jacobs, MD, PhD; Dirk R. Siewertsz van Reesema, MD; and Johannes W.J. Bijlsma, MD, PhD

Background: **Oral glucocorticoids combined with disease-modifying antirheumatic drugs are beneficial and retard radiologic joint damage in rheumatoid arthritis.**

Objective: **To investigate the clinical efficacy, disease-modifying properties, and side effects of low-dose glucocorticoids as monotherapy for previously untreated patients with early active rheumatoid arthritis.**

Design: **2-year randomized, double-blind, placebo-controlled clinical trial.**

Setting: **2 outpatient rheumatology clinics.**

Patients: **81 patients with early active rheumatoid arthritis who had not been treated with disease-modifying antirheumatic drugs.**

Intervention: **41 patients were assigned to 10 mg of oral prednisone per day, and 40 were assigned to placebo. Nonsteroidal anti-inflammatory drugs were allowed in both groups. After 6 months, sulfasalazine (2 g/d) could be prescribed as rescue medication.**

Measurements: **Clinical variables were assessed at baseline and every 3 months; radiologic studies were performed every 6 months. Adverse effects were documented every 3 months.**

Results: **In the first 6 months, the prednisone group showed more clinical improvement than the placebo group. This effect was not seen after 6 months except in grip strength and the 28-joint score for tenderness. Use of additional therapies was significantly less common in the prednisone group, particularly in the first 6 months. More than 65% of those who completed the study were not taking sulfasalazine. After month 6, radiologic scores showed significantly less progression in the prednisone group than in the placebo group. No clinically relevant adverse effects were observed, except for a higher incidence of osteoporotic fractures in the prednisone group.**

Conclusions: **Prednisone, 10 mg/d, provides clinical benefit, particularly in the first 6 months, and substantially inhibits progression of radiologic joint damage in patients with early active rheumatoid arthritis and no previous treatment with disease-modifying antirheumatic drugs. Because of their limited disease-modifying effects, glucocorticoids should be combined with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis.**

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For author affiliations, current addresses, and contributions, see end of text.
See editorial comment on pp 76-78.

Drug treatment for rheumatoid arthritis usually consists of a combination of a nonsteroidal anti-inflammatory drug (NSAID) and a disease-modifying antirheumatic drug (for example, sulfasalazine, methotrexate, gold salt, or a combination). New biological agents, such as tumor necrosis factor-α blocking agents and interleukin-1 receptor antagonists, appear promising (1, 2). Glucocorticoids have had a special place in the treatment of rheumatoid arthritis since the publication of the report by Hench and coworkers showing that cortisone dramatically alleviated the symptoms of rheumatoid arthritis by inhibiting inflammation (3). This period of enthusiasm in the 1950s was followed by a long period in which glucocorticoids were applied cautiously for rheumatoid arthritis because of their many side effects and the recognition that inhibition of inflammation is not necessarily associated with retardation of joint damage (4).

Ongoing research on glucocorticoids in rheumatoid arthritis focused on both inflammation and joint damage. Some recent studies showed that glucocorticoids reduced the progression of joint damage when added to therapy with disease-modifying antirheumatic drugs. These findings suggested that glucocorticoids might also have disease-modifying properties. If this could be confirmed, glucocorticoids might be used more often, especially since potential serious adverse effects of glucocorticoid therapy are more easily managed today (5). Secondary osteoporosis is inhibited by potent bisphosphonates, and gastrointestinal complications of glucocorticoid therapy, especially in combination with NSAIDs, can be reduced by misoprostol, proton-pump

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inhibitors, or cyclooxygenase-2 selective NSAIDs. As yet, disease-modifying properties of low-dose glucocorticoids as monotherapy for patients with early rheumatoid arthritis have not been investigated. The aim of our study was to investigate the clinical efficacy, disease-modifying properties, and side effects of low-dose glucocorticoids as monotherapy for previously untreated patients with early active rheumatoid arthritis.

METHODS

Patients

From October 1992 through October 1995, all consecutive outpatients at the rheumatology departments of the Deventer and Zutphen Hospitals, the Netherlands, who were at least 18 years of age and had early previously untreated rheumatoid arthritis (disease duration < 1 year) that satisfied classification criteria were invited to participate in the study (6). To be included, patients had to have active disease, which was defined as the presence of at least two of the following three criteria: 1) early-morning stiffness lasting 30 minutes or longer, 2) 28-joint score for tenderness and 28-joint score for swelling of 3 or more, and 3) Westergren erythrocyte sedimentation rate of 28 mm or higher after 1 hour (7, 8). Exclusion criteria were contraindications to prednisone or NSAIDs, active gastrointestinal problems, serious complicating diseases, severe hypertension, hemorrhagic diathesis, treatment with cytotoxic or immunosuppressive drugs, alcohol or drug abuse, and psychiatric or mental problems. Informed consent was obtained from all patients before participation. Of the 118 eligible patients, 37 declined to participate (**Figure 1**).

Intervention

Pharmacy personnel at Deventer Hospital used a computer-generated randomization procedure to randomly assign the 81 participating patients, in blocks of 10, to one of two treatment groups. One group received two tablets of prednisone, 5 mg, once daily at breakfast, and one group received placebo. The pharmacology department at Deventer Hospital prepared and labeled the prednisone and placebo tablets, which were identical in shape and color, and distributed them to patients in unlabeled boxes. Only the pharmacist could access the allocation table. Both groups of patients received 500 mg of elementary calcium in the evening.

The code of randomization was broken after 2 years of treatment, and the prednisone dosage was tapered. Surplus tablets of the study medication were counted at every visit, and adherence was satisfactory (96%). Use of NSAIDs was not regulated. Local glucocorticoid injections were permitted only when absolutely necessary. Physical therapy and additional use of paracetamol were allowed. After 6 months, sulfasalazine (2 g/d) could be prescribed as rescue medication. The decision to add sulfasalazine was made on clinical grounds (activity of rheumatoid arthritis).

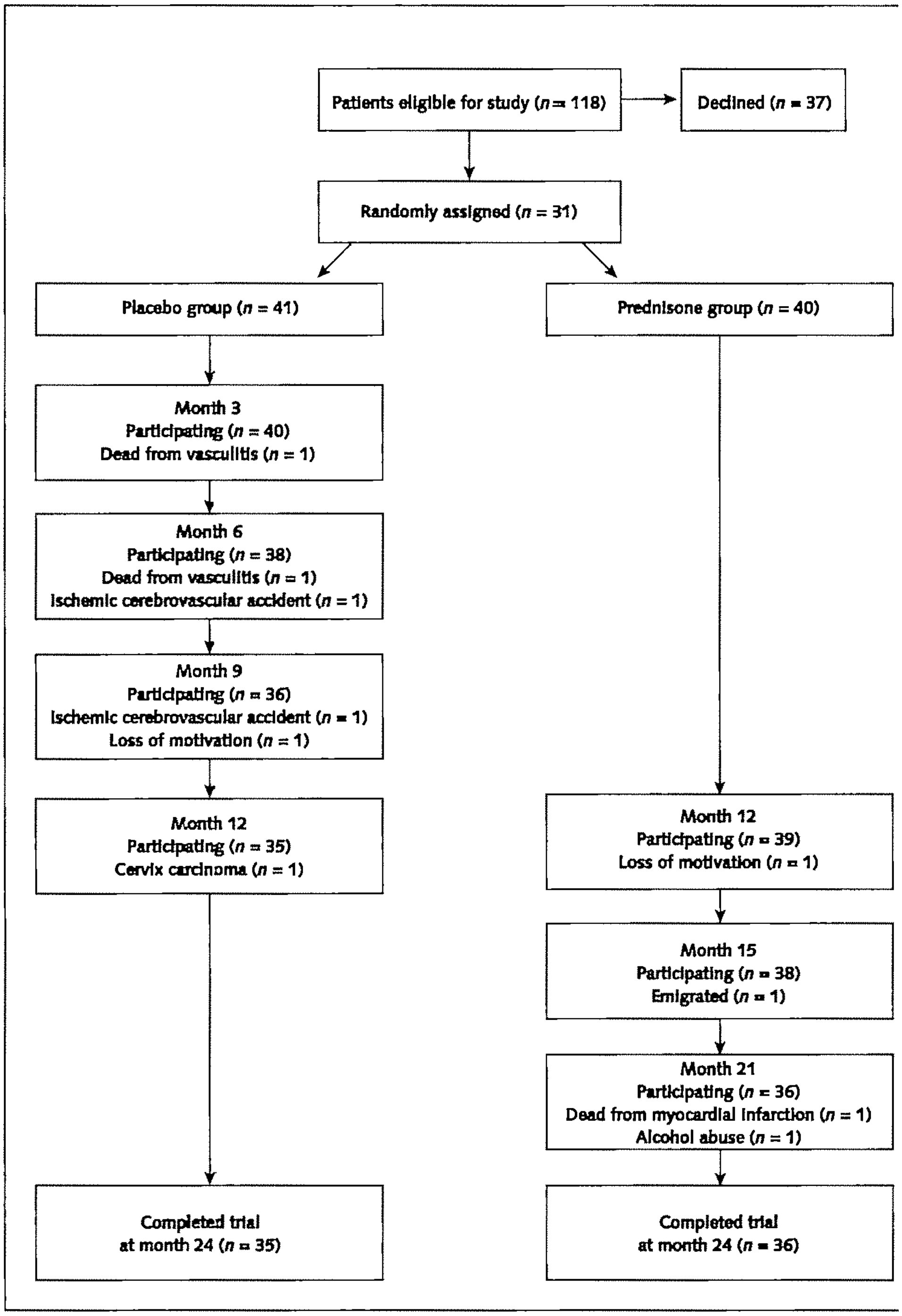
Design and Setting

The ethics committees of the University Medical Center Utrecht and the Deventer and Zutphen Hospitals approved the trial. The study was considered ethically acceptable when it was designed (1989–1991); later, however, it became clear that irreversible joint damage is an early feature of rheumatoid arthritis. With our present knowledge, it would probably be considered unethical to compare the effects of prednisone and placebo in patients who did not receive a disease-modifying antirheumatic drug for at least 6 months. In our study, sulfasalazine could be prescribed as rescue medication only after 6 months to avoid obscuring the effects of prednisone monotherapy.

Measurements

All clinical outcome measurements, except those for disability and radiologic outcomes, were performed at baseline and every 3 months. Disability, which was assessed with the Health Assessment Questionnaire, and radiologic outcomes were measured every 6 months. Early-morning stiffness was recorded in minutes (maximum, 720 minutes). Morning pain and general well-being were assessed on a horizontal visual analogue scale ranging from 0 to 100 mm, with 0 representing the best score (no problems) and 100 representing the worst score. Swelling and tenderness were assessed with the 28-joint score (7, 8). Grip strength was measured in kPa with a vigorimeter (range, 0 to 200 kPa); the mean of three measurements was calculated for each hand. Disability was assessed with a validated Dutch version of the Health Assessment Questionnaire (Vragenlijst Dagelijks Functioneren) (9), which had a range of 0 to 3 (0 represented the best score [no problems], and 3 represented

Figure 1. **Trial profile.**



the worst score). Serum C-reactive protein level was measured in mg/L.

To investigate the possible sparing effect of the trial medication, we recorded the use of NSAIDs and analgesics, the frequency of intra-articular corticosteroid injections, and the use of physiotherapy. The patients recorded the use of NSAIDs, analgesics, and physical therapy in standardized patient diaries. To calculate the use of NSAIDs and to compare different NSAIDs, we arbitrarily chose naproxen as a reference. One thousand mg of naproxen was defined as 1 unit and was considered to be approximately equivalent to 600 mg of azapropazone, 100 mg of diclofenac, 200 mg of flurbiprofen, 1600 mg of ibuprofen, 100 mg of indomethacin, 200 mg of ketoprofen, 15 mg of meloxicam, 1000 mg of nabumetone, 20 mg of piroxicam, and 600 mg of tiaprofenic acid. Every 3 months, the first author recorded use of intra-articular corticosteroid injections.

Radiologic outcome measures were erosions, joint space narrowing, and the total score for both (range, 0 to 448). The total score is the sum of the erosions and narrowing scores in 44 joints in the hands and feet, assessed on plain radiography and scored with the van der Heijde modification of the Sharp method (10, 11). Radiologic outcome measures also included the number of patients with erosive disease in each group and the number of radiologically affected joints per patient.

Radiographs were taken at entry and every 6 months. An assistant prepared the radiographs to be read, and all identifying patient data on the radiographs were concealed from the readers. The readers had no knowledge of patient identity when they scored the radiographs. Radiographs were read in random patient order and were scored for each patient in temporal order. Scoring in temporal order clearly has advantages, as a comparative study has shown (11). However, with this method, scores can either be stable or increase; a decrease (indicating improvement) is not possible. The first author and an independent radiologist viewed all available radiographs at one center. When the readers' total scores for individual cases differed by 25% or more, agreement was reached through discussion. Joint damage was defined as a score that exceeded 0. To correct for possible differences between the two treatment groups in the number of patients who developed little or no joint damage, we also analyzed data only from patients who developed joint damage. Furthermore, radiologic damage was also analyzed with a cutoff point of 4 modified Sharp units. A score of 0 to 3 was interpreted as no damage, and scores of 4 or greater were interpreted as joint damage. This cutoff point seems to reflect clinically relevant change (12) and was also used in our study to define erosive rheumatoid arthritis.

At the start of the study and every 3 months for 2 years, standardized lists were used to document adverse effects. We noted the occurrence of infections and the use of antibiotics; the latter was checked at the patient's pharmacy. For hypertension, the first author used a single device to measure blood pressure in mm Hg. For steroid diabetes, serum glucose level was measured in mmol/L. Hyperglycemia was defined according to the World Health Organization standard: postprandial, a glucose level of at least 11.0 mmol/L (198 mg/dL), and fasting, at least 6.6 mmol/L (119 mg/dL). Urinary glucose level was measured by using a semiquantitative method (dipstick). A value less than 2.7 mmol/L (49 mg/dL) was considered negative, a value of 2.7 to 5.5 mmol/L (50 to 99 mg/dL) was considered a trace, a value of 5.6 to 16.6 mmol/L (100 to 299 mg/dL) was considered 1+, a value of 16.7 to 54.9 mmol/L (300 to 989 mg/dL) was considered 2+, and a value of 55 mmol/L or greater (≥990 mg/dL) was considered 3+. To assess weight gain, body weight in kg was determined with a standardized scale. Gastrointestinal bleeding, ulcers, and peptic symptoms were documented, and the decision to perform gastroscopy was made clinically. Skin disorders were documented, and additional dermatologic expertise was requested when necessary. Hemogram and laboratory variables for kidney and liver function were assessed to monitor for hematologic and biochemical abnormalities. For eye disorders, symptoms and abnormalities were documented; when necessary, additional ophthalmologic expertise was requested. Neuropsychological disorders were recorded.

To assess for osteoporosis, we obtained a radiograph of the spine at baseline and every 6 months for 24 months. We examined vertebrae Th12 through L5. The first author and an independent rheumatologist scored the vertebrae blind, according to the method of Kleerekoper (13). This method is based on naked-eye inspection of the vertebrae and comparison of each vertebra with the vertebrae below and above. If an abnormal shape is noticed, the anterior, middle, and posterior heights of that particular vertebra are measured with a ruler. The mean of the heights measured by the two authors was used. The scoring system is as follows: 0 (normal shape and dimensions), 1 (only endplate deformity, middle height, <85%), 2 (anterior wedge deformity, anterior height, <85%), and 3 (compression deformity, all 3 heights, <85%) (13).

Statistical Analysis

All statistical analyses evaluating the effect of treatment were performed according to the intention-to-treat principle. For the 10 patients who withdrew during the study, the outcomes of the last measurements were carried forward, with the exception of the radiologic scores. For radiologic scores, missing data were estimated by using individual progression, as indicated by available scores; if the last measurements had been carried forward, the protective effect of medication on the joints would have been overestimated. Also, "on treatment" analyses were performed to validate the procedures used to estimate the missing data. For radiologic joint damage, which is in itself a cumulative score, and the secondary outcome measures (disability and grip strength), mean differences in changes from baseline between the two groups were tested at 24 months with two-sided *t*-tests or the Mann–Whitney U-test, where appropriate. For the other outcome measures, changes from baseline over time (24 months) were compared by using the change from baseline in the area under the curve (AUC) as a summary measure. This was done because baseline variables between the two groups favored the prednisone group, although the differences were not statistically significant (**Table 1**) (14). We divided the values for the change in AUC by the number of assessments at follow-up. Since the interval between assessments is identical (3 months), this makes the values for the change in AUC identical to the mean value of the changes occurring in each 3-month interval at follow-up. Therefore, the values for changes in AUC are easily interpretable.

The values for the change in AUC in both groups and the means of radiologic scores for each group at different points in time were tested for statistically significant differences by using unpaired two-sided *t*-tests or Mann–Whitney U-tests, where appropriate. We calculated the number of patients in each group who had clinically relevant improvement. Clinically relevant improvement was defined as at least 20% improvement in the 28-joint scores for swelling and tenderness and at least 20% improvement in at least two of the four following variables: pain, general well-being, Health Assessment Questionnaire score, and C-reactive protein level. In repeated-measurement analyses of variance, the clinical outcome measurements were used to analyze the relationship between time (disease course) and the effect of the medication (prednisone) on the clinical status of the patient. This allowed us to determine whether patients in the prednisone group showed improvement sooner than patients in the placebo group. To determine whether outcome measurements, patients' characteristics, side effects, and additional therapies statistically significantly differed between groups, we used unpaired, two-sided *t*-tests or Mann–Whitney U-tests, where appropriate, for the means and Fisher exact tests for proportions. Changes from baseline within groups were tested with paired *t*-tests or Wilcoxon signed-rank tests, where appropriate. All analyses were performed with the Number Cruncher Statistical System 97 (NCSS Statistical Software, Kaysville, Utah).

Table 1. **Baseline Characteristics of the 81 Patients with Early Rheumatoid Arthritis***

Characteristic	Prednisone Group (*n* = 40)	Placebo Group (*n* = 41)
Age, *y*	60 ± 14	64 ± 12
Male/female, *n/n*	17/23	12/29
IgM rheumatoid factor, *n*†	29	31
Erosive disease, *n*‡	16	15
Early-morning stiffness, *min*	100 ± 62	117 ± 71
Morning pain, *mm*§	28 ± 20	34 ± 25
General well-being, *mm*§	31 ± 23	41 ± 23
28-Joint score for swelling	7.3 ± 3.7	8.6 ± 4.3
28-Joint score for tenderness	8.9 ± 5.7	8.6 ± 5.0
Grip strength, *kPa*	49 ± 24	47 ± 24
Disability score‖	0.8 ± 0.6	1.0 ± 0.7
C-reactive protein level, *mg/L*	11 ± 18	20 ± 28
Radiologic score for hands and feet¶	11 ± 11	15 ± 21
Hypertension, *n***	5	11
Chronic obstructive pulmonary disease, *n*	1	2
History of documented peptic ulcer, *n*	1 (>10 years ago)	0
Peptic symptoms treated with medication, *n*	4	1
Cardiovascular disease, *n*	1 (coronary bypass)	0

* Values presented with a plus/minus sign are the mean ± SD. No statistically significant differences were seen between groups.

† Rheumatoid factor status was considered positive when the IgM rheumatoid factor level was ≥25 IU/mL. This cutoff point yielded a false-positive test result for <5% of the general population.

‡ A Sharp–van der Heijde erosion score of ≥4 was considered erosive, and a score of 0 to 3 was considered nonerosive.

§ Measured with the visual analogue scale. Morning pain and general well-being in the previous 48 hours were calculated on a scale from 0 to 100 mm, with 0 representing the best score (no problems) and 100 representing the worst score.

‖ Measured with a Dutch version of the Health Assessment Questionnaire (9). Scores ranged from 0 to 3, with 0 representing the best score (no problems) and 3 representing the worst score.

¶ Erosions and joint space narrowing were assessed by using the van der Heijde modification of the Sharp method (10, 11). Scores ranged from 0 (no damage) to 448 (maximum score for erosions and joint space narrowing in hands and feet).

** These patients were normotensive with medication at the start of the study.

Table 2. **Effects of Prednisone Treatment in Patients with Early Rheumatoid Arthritis**[*]

Variable	Prednisone Group (*n* = 40)	Placebo Group (*n* = 41)	95% CI for the Difference	*P* Value
Changes from baseline				
12 months				
Radiologic damage	8 ± 13	15 ± 15		0.008
Grip strength, *kPA*	13 ± 21	−1 ± 19	5 to 23	0.002
Functional disability[†]	0.1 ± 0.6	0.1 ± 0.6		>0.2
24 months				
Radiologic damage	16 ± 23	29 ± 26		0.007
Grip strength, *kPA*	13 ± 19	4 ± 24	0 to 19	0.05
Functional disability[†]	0.1 ± 0.7	0.0 ± 0.6		>0.2
Change in AUC at 24 months[‡]				
Early-morning stiffness, *min*	−43 ± 69	−28 ± 78		>0.2
Morning pain, *mm*[§]	−5 ± 17	1 ± 22	−2 to 15	0.14
General well-being, *mm*[§]	−1 ± 24	0 ± 18		>0.2
28-Joint score for swelling	−2 ± 4	−1 ± 4	−1 to 2	>0.2
28-Joint score for tenderness	−2 ± 4	0 ± 5	1 to 5	0.01
C-reactive protein level, *g/L*	−1 ± 15	−0 ± 24		>0.2
Individual patient improvement, *n/n* (%)[‖]				
At 12 months	13/40 (33)	10/41 (24)	−0.1 to 0.3	>0.2
At 24 months	12/40 (30)	9/41 (22)	−0.1 to 0.3	>0.2
Cumulative use of additional therapy				
Patients receiving physiotherapy, *n/n*				
At 6 months	7/40	12/41	−0.3 to 0.1	>0.2
At 24 months	12/40	19/41	−0.4 to 0.0	0.17
Physiotherapy sessions, *n*				
At 6 months	108	308		
At 24 months	701	771		
Patients receiving intra-articular corticosteroid injections, *n/n*[¶]				
At 6 months	2/40	11/41	−0.4 to −0.1	0.01
At 24 months	8/40	12/41	−0.3 to 0.1	>0.2
Injections, *n*				
At 6 months	2	21		
At 24 months	17	43		
Patients taking paracetamol, *n/n*[**]				
At 6 months	23/40	23/41	−0.2 to 0.2	>0.2
At 24 months	25/40	24/41	−0.2 to 0.3	>0.2
Paracetamol tablets, *n*				
At 6 months	772	2546		
At 24 months	4237	8334		

[*] Values presented with a plus/minus sign are the mean ± SD. Unpaired two-sided *t*-tests were used for normal distribution of the data, and Mann–Whitney U-tests were used for non-normal distribution; in the latter cases, no 95% CIs for the difference are given. AUC = area under the curve.

[†] Measured with a Dutch version of the Health Assessment Questionnaire. Scores ranged from 0 to 3, with 0 representing the best score (no problems) and 3 representing the worst score (9).

[‡] The values for the change in AUC were divided by the number of assessments at follow-up, making them identical (since the interval between assessments [3 months] is identical) to the mean value of the changes occurring in each 3-month interval at follow-up. This was done to simplify interpretation of the data.

[§] Measured with the visual analogue scale. Morning pain and general well-being in the previous 48 hours were assessed on a scale of 0 to 100 mm, with 0 representing the best score (no problems) and 100 representing the worst score.

[‖] Improvement is defined as ≥20% improvement in the 28-joint score for swelling and the 28-joint score for tenderness and ≥20% improvement in ≥2 of the 4 following variables: visual analogue scale score for pain, visual analogue scale score for general well-being, disability score, and C-reactive protein level.

[¶] A corticosteroid injection was defined as 40 mg of triamcinolone acetonide or equivalent.

[**] The use of nonsteroidal anti-inflammatory drugs is reported in Figure 2. Two patients in each group used additional analgesics (pentazocine, 50 mg; tramadol, 50 mg; or dextropropoxyphene, 150 mg).

RESULTS

Thirty-seven of 118 patients declined to participate in the study for the following reasons: a wish to become pregnant, concern about the side effects of glucocorticoids, the inconvenience of visits to the hospital outpatient department and frequent monitoring, and unwillingness to take the 50% risk for receiving placebo. Patients who declined to participate had a mean age (±SD) of 48 ± 12 years. Twenty-five were women, 28 had IgM rheumatoid factor, and 14 had erosive changes on radiographs of the hands or feet. Compared with study participants, patients who declined participation were younger and more likely to be women. Patient characteristics at the start of the study are shown in

Table 1. No statistically significant differences were seen between the two groups. All patients were white except for 2 patients in the prednisone group.

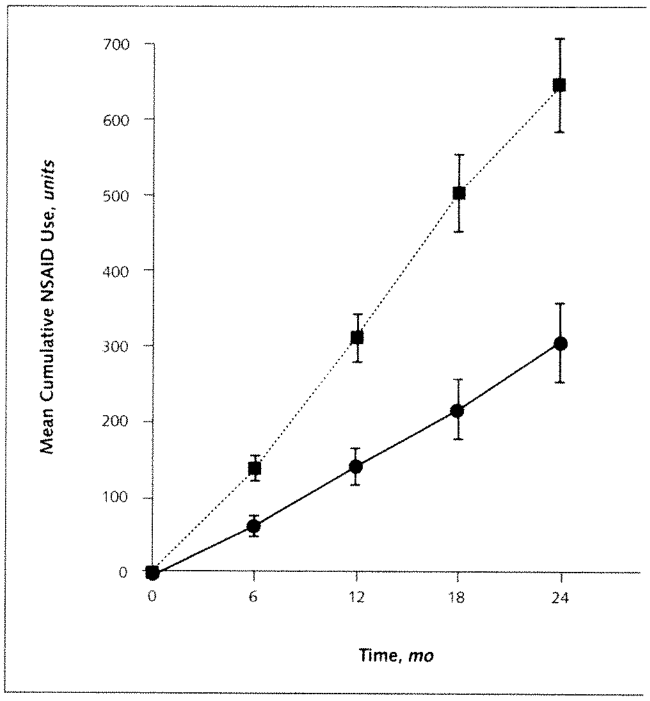
Ten patients withdrew from the study, 4 in the prednisone group and 6 in the placebo group (**Figure 1**). Patients in the prednisone group withdrew because of emigration (1 patient at 15 months), loss of motivation (1 patient at 12 months), alcohol abuse (1 patient at 21 months), and death from myocardial infarction (1 patient at 21 months). Patients in the placebo group withdrew because of cervix carcinoma (1 patient lost to follow-up at 12 months), ischemic cerebrovascular accidents that were attributed to arteriosclerosis (1 patient at 6 months and 1 patient at 9 months), loss of motivation (1 patient at 9 months), and rheumatoid arthritis vasculitis (1 patient who died at 3 months and 1 patient who died at 6 months despite aggressive immunosuppressive therapy). Of the 10 patients who withdrew, 1 patient in the prednisone group (alcohol abuse) and 1 in the placebo group (loss of motivation) received sulfasalazine as rescue medication at 15 and 6 months, respectively. No patients left the study because of adverse effects related to the study medication. After 6 months, 39 of the 71 patients who completed the study (20 in the placebo group and 19 in the prednisone group) received sulfasalazine as additional antirheumatic therapy.

Clinical Efficacy

For most clinical variables, the changes from baseline favored the prednisone group at 12 and 24 months but did not differ significantly between the two groups. Exceptions were grip strength and the 28-joint score for tenderness; for these variables, a larger, statistically significant improvement was seen in the prednisone group compared with the placebo group (**Table 2**). A statistically significant interaction of time and medication was seen for three clinical variables: pain, 28-joint score for tenderness, and grip strength. Plots of these variables in time showed that this was due to more rapid improvement during the first 6 months in the prednisone group than in the placebo group (data not shown). Individual patient improvement was 33% in the prednisone group and 24% in the placebo group at 12 months and 30% and 22%, respectively, at 24 months (**Table 2**).

Overall use of physiotherapy was significantly lower in the prednisone group than in the placebo group, especially in the first 6 months. At 24 months, the difference in the total number of sessions of physiotherapy was not as pronounced but continued to favor the prednisone group. In the first 6 months, 2 intra-articular corticosteroid injections were administered in the prednisone group and 21 were administered in the placebo group. The total number of intra-articular injections given in the prednisone group at 24 months was 40% lower than that in the placebo group. A total of 772 paracetamol tablets were taken in the first 6 months in the prednisone group compared with 2546 in the placebo group. At 24 months, use of paracetamol in the prednisone group was 49% lower than that in the placebo group. The overall use of NSAIDs over 24 months was also considerably lower in the prednisone group than in the placebo group (**Figure 2**).

Figure 2. **Cumulative mean use of nonsteroidal anti-inflammatory drugs (*NSAIDs*) in units.**

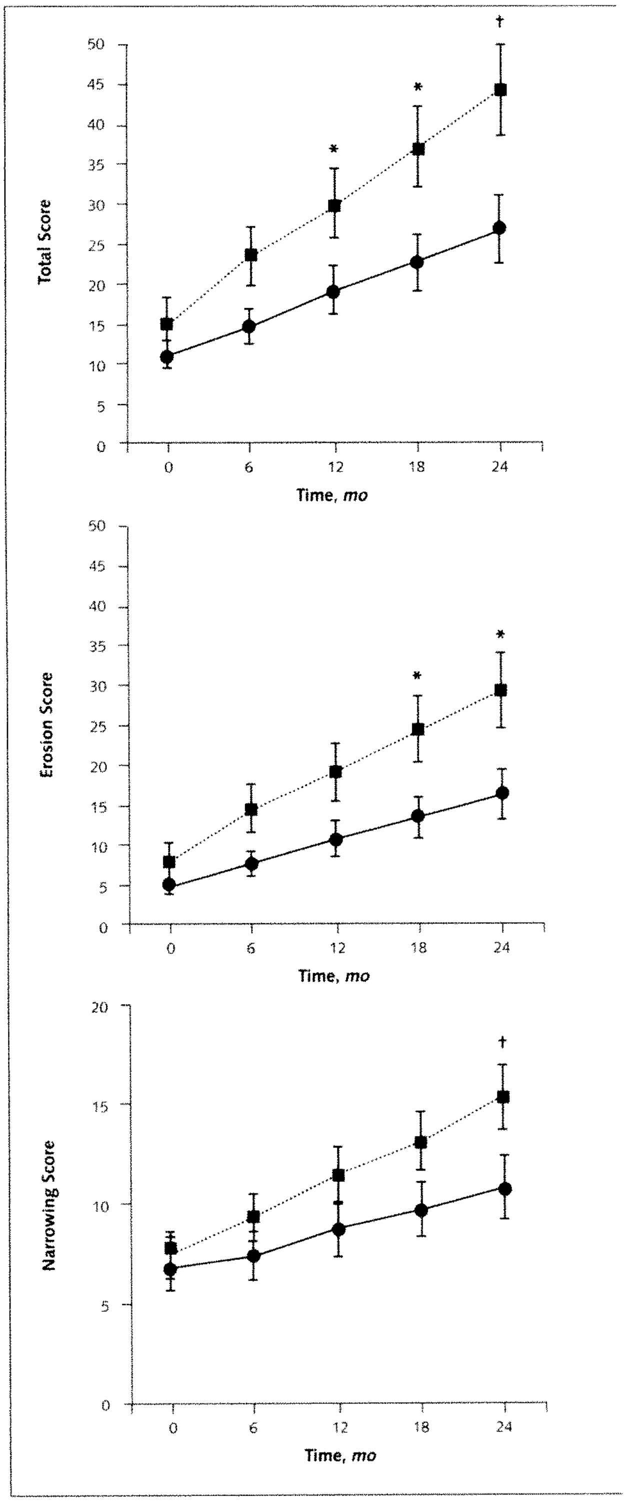


One unit = 1000 mg of naproxen or the equivalent dose of another NSAID. At follow-up at all points in time, statistically significant differences were seen between the two groups ($P < 0.001$ [Mann–Whitney U-test]). The solid line indicates the prednisone group; the dotted line indicates the placebo group. Error bars represent the standard error.

Disease-Modifying Properties

Fifty patients (24 in the prednisone group [60%] and 26 in the placebo group [63%]) had nonerosive

Figure 3. **Radiologic scores over time for both erosions and joint space narrowing in hands and feet (*top*), erosions alone (*middle*), and joint space narrowing alone (*bottom*).**



All scores are means and are based on the van der Heijde modification of the Sharp method (10, 11). Solid lines indicate the prednisone group; dotted lines indicate the placebo group. Error bars represent the standard error. *P = 0.04; †P = 0.02.

disease at the start of the study. At 24 months, 30% of patients in the prednisone group and 22% in the prednisone group still had nonerosive disease. At baseline, the mean total score for radiologic outcome measures (the combination of the scores for joint space narrowing and erosions) was slightly higher for the placebo group than for the prednisone group, although the difference was not statistically significant (**Table 1**). From month 12 on, radiologic scores showed significantly less progression in the prednisone group than in the placebo group. Mean changes (±SD) from baseline in modified Sharp scores were 8 ± 13 and 15 ± 15 at 12 months for the prednisone and placebo groups, respectively (P = 0.008; effect size, 0.52) and 16 ± 23 and 29 ± 26, respectively, at 24 months (P = 0.007; effect size, 0.56) (**Table 2**).

Radiologic scores over time are shown in **Figure 3**. At 12 months, the total mean score (±SD) for radiologic damage was 19 ± 19 for the prednisone group and 30 ± 28 for the placebo group (P = 0.04). At 24 months, the scores were 27 ± 28 and 44 ± 37, respectively (P = 0.02) (**Figure 3**, *top*). The mean score for erosions at 12 months was 11 ± 13 in the prednisone group and 19 ± 23 in the placebo group (P = 0.08). At 24 months, the scores were 16 ± 20 compared with 29 ± 30, respectively (P = 0.04) (**Figure 3**, *middle*). The mean scores for joint space narrowing were 9 ± 9 in the prednisone group and 11 ± 9 in the placebo group at 12 months (P = 0.06) and 11 ± 10 and 15 ± 10, respectively, at 24 months (P = 0.02) (**Figure 3**, *bottom*). The mean total numbers of affected joints per patient in the prednisone group and the placebo group were 10 ± 7 and 13 ± 8 at 12 months (P = 0.05) and 12 ± 9 and 16 ± 9 at 24 months (P = 0.047), respectively. Similar differences in all radiologic scores between the two groups were found by "on treatment" analyses (n = 71), analyses only of patients developing joint damage, and analyses of radiologic damage with a cutoff point of 4 (0 to 3, no damage; ≥4, joint damage) (data not shown).

Adverse Effects

We compared body weight, serum glucose levels, and blood pressure at the start of the study and after 24 months of treatment. In the prednisone group, the mean body weight (±SD) increased significantly from baseline, from 77 ± 19 kg to 80 ± 20 kg ($P = 0.001$). In the placebo group, no statistically significant change was seen. Also in contrast to the placebo group, the mean serum glucose level (±SD) increased significantly in the prednisone group, from 5.1 ± 0.6 mmol/L to 5.9 ± 1.9 mmol/L (92 ± 11 mg/dL to 106 ± 34 mg/dL) ($P = 0.01$). Hyperglycemia, as defined by the World Health Organization, developed in 2 patients in the prednisone group and 1 in the placebo group. The other variables did not change significantly in either group. At the start of the study, 1 patient in each group had one vertebral fracture (from Th12 to L5). After 24 months, the number of new vertebral fractures was higher in the prednisone group than in the placebo group. Five patients in the prednisone group had new fractures in the spine; of these 5 patients, 3 had a single fracture and 2 had two fractures. The patient in the prednisone group with a fracture at baseline did not develop new fractures. In the placebo group, 2 patients had new vertebral fractures. One was the patient with a fracture at baseline who developed another fracture; the other patient developed three fractures. Except for one osteoporotic fracture of the pelvis in the prednisone group, no osteoporotic fractures outside the spine (forearms, ribs, pelvis, or hips) were seen (Table 3).

Table 3. **Adverse Effects and Complications**

Adverse Effect or Complication	Events in the Prednisone Group (*n* = 40)	Events in the Placebo Group (*n* = 41)
	n	
Infections treated with antibiotics, *n*/*n**		
Skin	0	5 (4 patients)
Respiratory tract	13 (11 patients)	13 (9 patients)
Intestinal tract†	1	2
Urinary tract	3 (2 patients)	2
Gastrointestinal		
Stomatitis‡	0	1
Nausea/vomiting	2	2
Peptic symptoms leading to gastroscopy	7	3
Ulcer with bleeding on gastroscopy	1	2
Diarrhea	0	2
Cardiovascular		
Newly developed hypertension	7	6
Angina pectoris	3	3
Myocardial infarction§	1	0
Ischemic cerebrovascular accident‖	0	2
Arterial occlusion in legs	0	1
Calf vein thrombosis	0	2
Heart rhythm disorders	1	2
Congestive heart failure	1	1
Ankle edema	1	0
Skin (excluding infections)		
Ulcus cruris	3	2
Exanthema	2	1
Petechiae	1	1
Ophthalmologic		
Glaucoma	1	0
Cataract	1	1
Vitreous humor hemorrhage¶	1	0
New osteoporotic fractures**		
Vertebral	7 (5 patients)	4 (2 patients)
Peripheral (pelvis)	1	0
Miscellaneous		
Impotence††	0	2
Depression	1	2
Concentration disorders	0	1
Cervix carcinoma‡‡	0	1
Medication-dependent diabetes mellitus	2	1
Systemic vasculitis§§	0	2

* The number of infections not treated with antibiotics, such as the common cold, was similar in both groups.

† No cultures were taken.

‡ Stomatitis was caused by allergy, probably to a nonsteroidal anti-inflammatory drug used, according to the patient's dermatologist.

§ Cause of death. The patient was 76 years of age.

‖ Cause of withdrawal from the study. The patients were 72 and 73 years of age.

¶ Probably not related to the study medication.

** Vertebral fractures Th12 to L5, assessed according to the Kleerekoper method (13). At the start of the study, one patient in each group had a vertebral fracture.

†† Impotence was not included in the standardized diary but was spontaneously reported by these two patients.

‡‡ Cause of withdrawal from the study.

§§ Cause of death. The patients were 62 and 78 years of age.

Other adverse effects are shown in Table 3. There were minor infections in both groups. Patients in the prednisone group had no serious skin infections, but erysipelas was seen five times in 4 patients in the placebo group. The numbers of infections in the respiratory, gastrointestinal, and urinary tracts were approximately equal in the two groups. Three patients (1 in the prednisone group and 2 in the placebo group) developed peptic ulcer disease with bleeding, which was confirmed by gastroscopy. The numbers of patients with newly developed hypertension during the study were approximately equal (7 in the prednisone group and 6 in the placebo group). At the start of the study, 11 patients in the placebo group and 5 in the prednisone group were normotensive because of medication for essential hypertension, and they remained stable during the study. In the prednisone group, 1 patient (76 years of age) died after 21 months of a myocardial infarction (confirmed at autopsy). During the study, 3 patients (2 in the prednisone group and 1 in the placebo group) developed diabetes mellitus, which was managed with oral antidiabetic agents and diet; no insulin treatment was needed. Except for infections, the two groups had an equal number of adverse effects affecting the skin, which were well controlled with conservative treatment. Serum aminotransferase levels were elevated in 1 patient in the prednisone group and 1 in the placebo group; values were less than two times the upper limit of normal. Mean serum creatinine concentration did not increase during the study in either group. No other biochemical or hematologic abnormalities were seen during the study. One patient in the prednisone group had glaucoma that was well controlled with conservative treatment, and 1 patient in each group had a cataract. One patient in the prednisone group had a hemorrhage in the vitreous humor in the right eye that caused partial loss of vision, but this complication was probably unrelated to the study medication. No disorders of the central nervous system were observed. For patients with newly developed depressive symptoms (1 in the prednisone group and 2 in the placebo group), no medication was needed.

DISCUSSION

The Medical Research Council and Nuffield Foundation trials in the mid-1950s and mid-1960s suggested a possible disease-modifying role for glucocorticoids. It is difficult to interpret the results of these trials, however, because of the heterogeneity of the patient groups, the long duration of disease at the start of the studies, confounding by indication, and multiple concomitant therapies. In 1995, in a double-blind, placebo-controlled study of 128 patients with early rheumatoid arthritis (average disease duration, 1.3 years), Kirwan demonstrated a significant reduction in progression of radiologic joint damage in the hands when glucocorticoids were added to antirheumatic treatment (15). Patients received prednisone (7.5 mg/d) or placebo for 2 years in addition to NSAIDs (95% of patients) and disease-modifying antirheumatic drugs (71% of patients). After 2 years, both the total number of new erosions and the number of patients with erosions were significantly lower in the glucocorticoid group. Clinical variables improved only during the first year of therapy. Kirwan concluded that a fixed daily dose of 7.5 mg of prednisone given as adjuvant therapy for early active rheumatoid arthritis retards radiologic progression of joint destruction. However, only hands were evaluated for the radiologic score. In a 1998 follow-up study by Hickling and coworkers (16), joint destruction resumed after the prednisone dosage was tapered and therapy was discontinued.

In 1996, Saag and associates (17) reviewed the literature systematically and performed a meta-analysis of the effectiveness of low-dose glucocorticoids in rheumatoid arthritis. Glucocorticoids seemed to be at least as effective as other therapies in improving disease activity. However, data were limited because the treatment episodes were relatively short (7 months on average) and glucocorticoids were given late in the disease course, often in combination with disease-modifying antirheumatic drugs.

In a randomized study of early rheumatoid arthritis, Boers and colleagues (18) compared the effect of sulfasalazine monotherapy with that of combined therapy with prednisone, methotrexate, and sulfasalazine. Prednisone was started at an initial dosage of 60 mg/d, which was tapered in six steps over 6 weeks to 7.5 mg/d, and was withdrawn at week 28. The combined therapeutic regimen slowed radiologic damage significantly more than sulfasalazine alone at weeks 28, 56, and 80. Haagsma and coworkers (13) and Dougados and associates (19), however, found no differences in effect between sulfasalazine and the combination of sulfasalazine and methotrexate in patients with rheumatoid arthritis. Therefore, the difference in effectiveness between combination therapy and sulfasalazine in the study by Boers and colleagues was probably due to the effect of prednisone. In addition, the combined therapy offered better disease control. In contrast to our present study, the cohort of patients with rheumatoid arthritis in the study by Boers and colleagues was younger and had more active disease. Patients received prednisone at an initial dosage of 60 mg/d, which was tapered; treatment was stopped at 28 weeks. During that 1-year study, the effect of combination therapy on progression of joint destruction persisted after 28 weeks but clinical remission ended in most patients.

Our study is unique because it did not include concomitant therapy with disease-modifying antirheumatic drugs at study entry. We were therefore able to assess the effects of steroids on joint damage independent of disease-modifying antirheumatic drugs. In our study, most patients taking low-dose prednisone needed less additional therapy and showed temporary improvement in most disease variables when compared with the placebo group, although the differences were not statistically significant for all variables. This may be due to more intensive use of additional therapies, including NSAIDs, in the control group (**Table 2** and **Figure 2**). The clinical improvement seen in the studies by Kirwan (15) and by Boers and colleagues (18) lasted longer, for more than 6 months but less than 1 year, at which point the treatment groups no longer differed from the control groups. Compared with prednisone as monotherapy, combination of glucocorticoids with disease-modifying antirheumatic drugs or biological agents in early active rheumatoid arthritis might prolong the clinical benefit. The remarkable retardation of radiologically detected joint destruction in our study was similar to that observed in the studies by Kirwan (15) and by Boers and colleagues (18). The difference between the two groups in our study even increased gradually until the end of the second year. We do not advocate use of glucocorticoids as monotherapy, however. In our opinion, glucocorticoids, because of their limited disease-modifying effects, should be combined with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis.

In our study, glucocorticoid-induced osteoporosis was a major side effect. We prescribed calcium supplementation for all patients, but if we were performing this study today, we would use more intensive treatment, such as bisphosphonates. This would probably result in fewer signs and symptoms of osteoporosis.

Glucocorticoids suppress a wide variety of nonspecific inflammatory responses (such as cell trafficking and prostaglandin production), as well as specific immune processes, with emphasis on cytokine modulation. At a cellular level, glucocorticoids inhibit the access of leukocytes to inflammatory sites; modulate the functions of leukocytes, endothelial cells, and fibroblasts; inhibit the production and functioning of a variety of proinflammatory cytokines while enhancing the production of anti-inflammatory mediators; and suppress the synthesis of cartilage-degrading metalloproteases by fibroblasts and articular chondrocytes. Taken together, these effects induce the marked clinical amelioration of rheumatoid arthritis (21) and may also explain the protection of bone and cartilage against inflammation-induced degradation, which in turn may explain the drugs' disease-modifying properties.

In conclusion, low-dose prednisone alleviates symptoms of rheumatoid arthritis and has disease-modifying properties. Further investigation of long-term low-dose glucocorticoid therapy in rheumatoid arthritis that examines not only symptoms but especially joint damage and functional outcome is needed.

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Risk Factors for *Helicobacter pylori* Resistance in the United States: The Surveillance of *H. pylori* Antimicrobial Resistance Partnership (SHARP) Study, 1993–1999

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Background: **Pretreatment antimicrobial resistance has an important impact on the efficacy of many *Helicobacter pylori* treatment regimens.**

Objective: **To estimate the prevalence of *H. pylori* resistance to antimicrobials in the United States, to characterize risk factors associated with *H. pylori* antimicrobial resistance, and to explore the association between drug utilization and antimicrobial resistance patterns over time.**

Design: **Meta-analysis using patient-level data.**

Setting: **20 nationwide trials of *H. pylori* eradication.**

Patients: **3624 men and women, each of whom contributed one isolate.**

Measurements: **Rates of *H. pylori* resistance to clarithromycin, metronidazole, and amoxicillin, according to geographic region, age, sex, study year, ethnicity, ulcer status, test method, and study.**

Results: **Overall resistance to clarithromycin, metronidazole, and amoxicillin was 10.1% (95% CI, 9.1% to 11.1% [360 of 3571 patients]), 36.9% (CI, 35.1% to 38.7% [1063 of 2883 patients]), and 1.4% (CI, 1.0% to 1.8% [48 of 3486 patients]), respectively. In multivariable analyses, multiple risk factors were associated with resistance to individual agents. Clarithromycin resistance was significantly associated with geographic region ($P = 0.050$), older age ($P < 0.001$), female sex ($P < 0.001$), inactive ulcer disease ($P < 0.001$), and study ($P = 0.010$). Metronidazole resistance was significantly associated with female sex ($P < 0.001$), earlier year of study enrollment ($P = 0.036$), Asian ethnicity ($P < 0.001$), use of an epsilometer test ($P = 0.002$), and study ($P < 0.001$). Amoxicillin resistance was low and was not significantly associated with any risk factor. In the 1990s, when rates for use of oral macrolides and metronidazole were relatively stable, clarithromycin resistance rates were stable and metronidazole resistance rates varied.**

Conclusions: **Clinicians should consider risk factors for antimicrobial resistance when deciding which patients should have susceptibility testing and when choosing appropriate *H. pylori* treatments in the empirical setting.**

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Helicobacter pylori is the major pathologic agent in the development of gastric and duodenal ulcers, and *H. pylori* eradication is known to reduce recurrence of peptic ulcers (1). In addition, infection has been linked to chronic active gastritis, gastric carcinoma, mucosa-associated lymphoid-tissue lymphoma, and possibly nonulcer dyspepsia. Pretreatment antimicrobial resistance has an important negative impact on the efficacy of many *H. pylori* treatment regimens. Although researchers have attempted to evaluate *H. pylori* resistance in the United States (2–4), risk factors associated with antimicrobial resistance have not been well characterized. Identification of such risk factors is of particular interest in *H. pylori* infection, for which treatment is usually prescribed without knowledge of the susceptibility of the individual patient's isolate.

Using patient-level data, we performed a meta-analysis to estimate the prevalence of *H. pylori* resistance to clarithromycin, metronidazole, and amoxicillin in the United States. The data were obtained from patients with ulcers who were enrolled in clinical trials between 1993 and 1999. We also attempted to characterize risk factors associated with antimicrobial resistance to *H. pylori* and explored the association between drug use and antimicrobial resistance patterns over time.

METHODS

The U.S. Food and Drug Administration (FDA) invited pharmaceutical companies that had *H. pylori* development programs to assist in developing a program for evaluating pretreatment *H. pylori* antimicrobial resistance in patients with ulcers. The study was called the Surveillance of *H. pylori* Antimicrobial Resistance Partnership (SHARP). The pharmaceutical companies provided information that had previously been submitted

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to support a new drug application or was obtained from other in-house data.

The FDA requested the following data: study number, patient identification number, date of culture, state in which the patient was enrolled, age, sex, ethnicity, ulcer status (active vs. inactive ulcer at baseline), method used to test for clarithromycin susceptibility, pretreatment clarithromycin minimal inhibitory concentration (MIC), method used to test for metronidazole susceptibility, pretreatment metronidazole MIC, method used to test for amoxicillin susceptibility, and pretreatment amoxicillin MIC.

For our study, we included trials in which isolates were collected from patients with active or inactive peptic ulcer disease. According to study protocol, an active ulcer was defined endoscopically as a break in the mucosa of greater than 3 mm. Patients were considered to have inactive ulcers if they had had ulcer disease (confirmed with endoscopy or radiography) in the past 5 years. We included only trials that enrolled patients in the United States or Puerto Rico.

Susceptibility testing was performed at one of two major laboratories with expertise in culturing *H. pylori* (Veteran Affairs Medical Center–Baylor College of Medicine and Microbiology Specialists, Inc., both in Houston, Texas). At least one MIC value obtained by agar dilution or epsilometer test (also called E-test) had to be reported for clarithromycin, metronidazole, or amoxicillin. We used only one isolate from each patient for our analysis. When MIC results were available for antrum and corpus biopsy specimens, the higher of the two values was selected. In 1 of the 20 included trials, susceptibility testing was performed by both agar dilution and E-test. In 106 patients, MIC results were available by both methods for all three drugs. For these patients, only results obtained by agar dilution were included because agar dilution is the testing method preferred by the National Committee for Clinical Laboratory Standards (NCCLS).

The NCCLS interpretative criteria for agar dilution were used to classify the susceptibility of isolates to clarithromycin. An MIC less than or equal to 0.25 µg/mL indicated susceptibility, and an MIC of at least 1 µg/mL indicated resistance (5). The E-test strip allows MICs that may not correspond to standard twofold dilutions obtained by agar dilution; therefore, the criterion for intermediate susceptibility by agar dilution was modified from 0.5 µg/mL to a range of greater than 0.25 µg/mL to less than 1 µg/mL.

Because the NCCLS has not set interpretative criteria for susceptibility of *H. pylori* isolates to metronidazole, we used NCCLS criteria for anaerobes; an MIC less than or equal to 8 µg/mL indicated susceptibility and an MIC of at least 32 µg/mL indicated resistance. This resistance breakpoint has been correlated with treatment failures in patients receiving clarithromycin, metronidazole, and omeprazole (6). The intermediate category was modified from 16 µg/mL to a range of greater than 8 to µg/mL to less than 32 µg/mL. This allowed us to correlate E-test values with values obtained by agar dilution. In the analysis of resistance rates by risk factor, we did not use an intermediate category for clarithromycin or metronidazole. Isolates that fell into the intermediate range were classified as susceptible.

A resistance breakpoint for amoxicillin has not been determined. Isolates were considered susceptible if the MIC was less than or equal to 0.25 µg/mL (7) and were considered resistant if the MIC exceeded 0.25 µg/mL. In two trials, ampicillin was used in place of amoxicillin for susceptibility testing with the E-test. Ampicillin and amoxicillin are generally considered to behave the same way in vitro, and the NCCLS states that ampicillin is considered the class representative for amoxicillin and ampicillin (5).

Differences in resistance rates between agar dilution and the E-test were assessed by using the chi-square test. Relationships between individual risk factors and antimicrobial resistance were assessed by using the Pearson chi-square test, the Fisher exact test (using Monte Carlo estimation), and the Wald test from univariate logistic regression models for the continuous variables (age and year).

Meta-analysis was used to combine information about the relationship between *H. pylori* resistance and eight risk factors (geographic region, age, sex, year of enrollment, ethnicity, ulcer status, test method, and study). A fixed-effects model was implemented by fixed-effects multivariable logistic regression with an indicator variable for study in all regression models. In the full multivariable model, significance was defined as a *P* value less than 0.05. Method of susceptibility testing was included in the model because of the recognized difference in results for metronidazole between the E-test and agar dilution. Study-by-covariate interactions were examined and found to be nonsignificant ($P > 0.2$). Odds ratios and 95% CIs were calculated from the multivariable logistic regression models. These odds ratios allowed us to compare differences between levels of each risk factor while controlling for all other variables of interest. The odds ratio for age was calculated per 10 years of life (for example, 40 years vs. 30 years), and the odds ratio for year was calculated in steps of 1 year (for example, 1994 vs. 1993).

Since unadjusted proportions can be confounded by many factors, we calculated predicted rates of antimicrobial resistance in an attempt to standardize for a reference or "average" patient. The full multivariable logistic regression models were used to predict resistance rates and associated 95% CIs for each level of each risk factor. An "average" patient was assumed to be a 48-year-old white man from the southwestern United States with an active ulcer who was seen in 1996 in study 11 and whose isolate was tested by using agar dilution. Risk factors for the "average" (reference) patient were selected on the basis of the subpopulation with the largest sample size for geographic region, sex, ethnicity, ulcer status, and test method. The mean age and median year of enrollment were used. We also selected a reference study, which included the greatest number of patients who had the other reference demographic risk factors.

Predicted relative risks were calculated from the predicted resistance rates for clarithromycin and metronidazole. The predicted resistance rates for age in patients younger than 40 years, 40 to 65 years, and older than 65 years were based on a 35-year-old patient, a 48-year-old patient, and a 70-year-old patient, respectively. The predicted relative risk for age was calculated by comparing a 58-year-old patient with a 48-year-old patient, and the predicted relative risk for year was calculated by comparing 1997 with 1996.

For amoxicillin, relative risks were not calculated. The odds ratio was a good estimate of the relative risk because the overall resistance rates for amoxicillin are low. Odds ratios could not be calculated by geographic region for amoxicillin because no cases of resistance were reported in the northeastern United States. With the exception of the risk factor under consideration, all of the covariates were fixed at the previously described levels for prediction. Since results for the predicted rates and predicted relative risks were standardized to the specified "average" patient, a selection of different covariate patterns may have produced different prediction results.

The parametric bootstrap (8) was used to estimate 95% CIs around the predicted relative risks. Ten thousand bootstrap samples were taken from a multivariate normal distribution. The mean vector was given by the maximum likelihood estimators of the regression coefficients, and the covariance matrix was given by the estimated covariance matrix of the regression coefficients, both from the full multivariable logistic regression model. The percentile method was then used to calculate 95% CIs. The 95% CI around the predicted relative risk can also be thought of as a 95% posterior, or credible, interval if it is assumed that the prior distribution for each regression coefficient is noninformative (9–11).

Univariate analyses were conducted by using JMP statistical software, version 3.2.5 (SAS Institute, Inc., Cary, North Carolina). Multivariable analyses were conducted by using SAS, version 6.12 (SAS Institute, Inc.). Bootstrap calculations were performed by using S-PLUS 2000 (MathSoft, Inc., Cambridge, Massachusetts).

To evaluate the relationship between *H. pylori* resistance to clarithromycin or metronidazole and oral antimicrobial use in the general population, information from the IMS Health database was analyzed. IMS Health Incorporated (Plymouth Meeting, Pennsylvania) is a proprietary data collecting company that uses drug utilization data to monitor trends and use of pharmaceuticals. By using combined data from Provider Perspective and Retail Perspective Online (IMS Health), IMS Health provided the projected total number of extended units (for example, the number of individual tablets or capsules) of solid oral formulations of macrolides (erythromycin, clarithromycin, and azithromycin) and metronidazole purchased by "specific channels" in the United States from 1994 through 1999. Data from 1993 were not available for comparison. Specific channels in the combined database included independent pharmacies, chain pharmacies, mass merchandisers with and without pharmacies, proprietary stores (without pharmacies), food stores with pharmacies, nonfederal hospitals, federal facilities, clinics, and long-term care facilities.

Participating companies supplied the FDA with susceptibility data from previously conducted clinical trials. No funding was obtained for this study.

Table 1. **Summary of Clinical Trials Included in the Analysis***

Study Number (Reference)	Patients	States	Regions	Year	Mean Age (Range)	Sex	
						Male	Female
	n				*y*	%	
1 (12)	182	21	C, MA, MW, NE, NW, P, S, SE, SW	1993–1994	50 (20–84)	67	33
2 (12)	187	16	C, MA, MW, NE, NW, P, S, SE, SW	1993–1994	47 (18–77)	70	30
3 (13)	70	12	C, MW, NE, NW, S, SE, SW	1994	48 (26–73)	76	24
4 (14)	185	21	C, MA, MW, NE, NW, S, SE, SW	1994–1995	47 (20–80)	71	29
5 (15)	283	25	C, MA, MW, NE, NW, P, S, SE, SW	1994–1995	51 (22–84)	72	28
6 (16)	240	25	C, MA, MW, NE, NW, P, S, SE, SW	1995–1996	47 (22–81)	65	35
7 (15)	223	21	C, MA, MW, NE, NW, P, S, SE, SW	1995–1996	48 (19–78)	71	29
8 (15)	123	22	C, MA, MW, NE, NW, P, S, SE, SW	1996	51 (20–77)	64	36
9 (17)	144	13	C, MA, P, S, S, SW	1996	48 (22–82)	67	33
10 (17)	129	17	C, MA, NE, NW, P, S, SE, SW	1996	46 (22–86)	67	33
11 (18)†	131	20	C, MA, MW, NE, NW, S, SE, SW	1996	49 (21–84)	68	32
12 (17)	167	21	C, MA, MW, NE, NW, P, S, SE, SW	1996	52 (20–82)	59	41
13 (19)	50	14	C, MW, NE, NW, P, S, SE, SW	1996–1997	53 (24–85)	64	36
14 (20)	218	21	C, MA, MW, NE, NW, P, S, SE, SW	1997–1998	47 (18–86)	61	39
15 (20)	70	21	C, MA, MW, NE, NW, S, SE, SW	1997–1998	53 (18–87)	41	59
16 (4)	413	23	C, MA, MW, NE, NW, P, S, SE, SW	1997–1999	49 (18–83)	65	35
17 (21)	50	12	C, MA, NE, S, SE, SW	1998	49 (26–77)	68	32
18 (21)	311	29	C, MA, MW, NE, NW, P, S, SE, SW	1998–1999	48 (19–78)	64	36
19 (21)	82	10	C, MA, MW, NE, NW, S, SE, SW	1998–1999	40 (21–70)	60	40
20 (4)	366	26	C, MA, MW, NE, NW, P, S, SE, SW	1998–1999	46 (20–84)	64	36

* C = Central; MA = mid-Atlantic; MW = Midwest; NE = Northeast; NW = Northwest; P = Great Plains, S = South; SE = Southeast; SW = Southwest.

† In this trial, susceptibility testing for all three drugs was performed by both E-test and agar dilution. In 106 patients, for whom results from both methods were available, only the results from agar dilution were included.

RESULTS

Susceptibility

We compiled susceptibility data from 20 nationwide clinical trials conducted by six pharmaceutical companies from 1993 to 1999. The study characteristics of each trial are summarized in **Table 1** (4, 12–21). Predicted antimicrobial resistance rates by study for the 20 included trials are shown in **Figure 1**. Eradication results from 12 of these 20 studies have been published elsewhere (4, 13, 14, 16–18, 21). Overall, isolates from 4018 patients were collected. Isolates with at least one MIC value reported were available from 3624 patients (90%).

The in vitro susceptibilities to clarithromycin, metronidazole, and amoxicillin overall and according to test method (agar dilution or E-test) are listed in **Table 2**. Overall resistance to clarithromycin, metronidazole, and amoxicillin was 10.1% (95% CI, 9.1% to 11.1% [360 of 3571 patients]), 36.9% (CI, 35.1% to 38.7% [1063 of 2883 patients]), and 1.4% (CI, 1.0% to 1.8% [48 of 3486 patients]), respectively. Results for clarithromycin resistance were similar with either method. However, metronidazole resistance was significantly higher with the E-test than with agar dilution (22 percentage points [CI, 18.5 to 25.5 percentage points]; $P < 0.001$). The E-test was used for metronidazole in trials that enrolled patients from 1994 to 1996. In 1993 and from 1997 to 1999, only agar dilution was used. When we analyzed only the 3 years in which E-testing was performed, the results for agar dilution did not change (25.8% [126 of 489 patients]). The difference in resistance rates between the two testing methods was 0.7 percentage points (CI, −0.1 to 1.7 percentage points), which bordered on significance for amoxicillin ($P = 0.054$).

Risk Factor Analyses

For each of the eight risk factors, we present unadjusted and predicted antimicrobial resistance rates for an "average" patient (**Table 3**). *P* values are presented for the full multivariable model. Predicted resistance rates for clarithromycin and metronidazole were lower than the unadjusted rates for all risk factors evaluated, except year of enrollment (both drugs) and use of the E-test (metronidazole). In contrast, for amoxicillin, predicted resistance rates were higher than unadjusted rates for all risk factors. Given the low overall rates of amoxicillin resistance, the predicted resistance rates may have been

Table 1—**Continued**

Ethnicity					Ulcer Status		Susceptibility Test			Laboratory
Asian	Black	Hispanic	White	Other	Active	History	Clarithromycin	Metronidazole	Amoxicillin	
←			%			→				
3	24	0	69	4	100	0	Agar	Agar	Agar	A
1	33	0	54	12	100	0	Agar	Agar	Agar	A
7	23	10	60	0	100	0	E-test	E-test	E-test	A
2	25	7	65	1	86	14	E-test	E-test	E-test	B
7	21	6	64	2	81	19	E-test	E-test	E-test	B
2	25	16	53	4	89	11	E-test	E-test	E-test	B
3	22	12	60	3	0	100	E-test	E-test	E-test	B
8	18	11	63	0	81	19	E-test	E-test	E-test	B
1	23	0	76	0	100	0	E-test	E-test	E-test	A
2	29	0	67	2	100	0	E-test	E-test	E-test	A
5	18	21	53	3	86	14	Agar and E-test	Agar and E-test	Agar and E-test	B
5	22	0	49	24	0	100	Agar	Agar	Agar	A
2	28	0	70	0	0	100	Not done	Agar	Not done	A
3	17	0	41	39	100	0	Agar	Not done	Agar	A
0	9	0	61	30	0	100	Agar	Not done	Not done	A
3	17	25	52	3	73	27	Agar	Agar	Agar	A
0	44	0	54	2	74	26	Agar	Not done	Agar	A
3	25	0	70	2	79	21	Agar	Not done	Agar	A
2	30	0	66	2	91	9	Agar	Not done	Agar	A
2	28	24	45	1	78	22	Agar	Agar	Agar	A

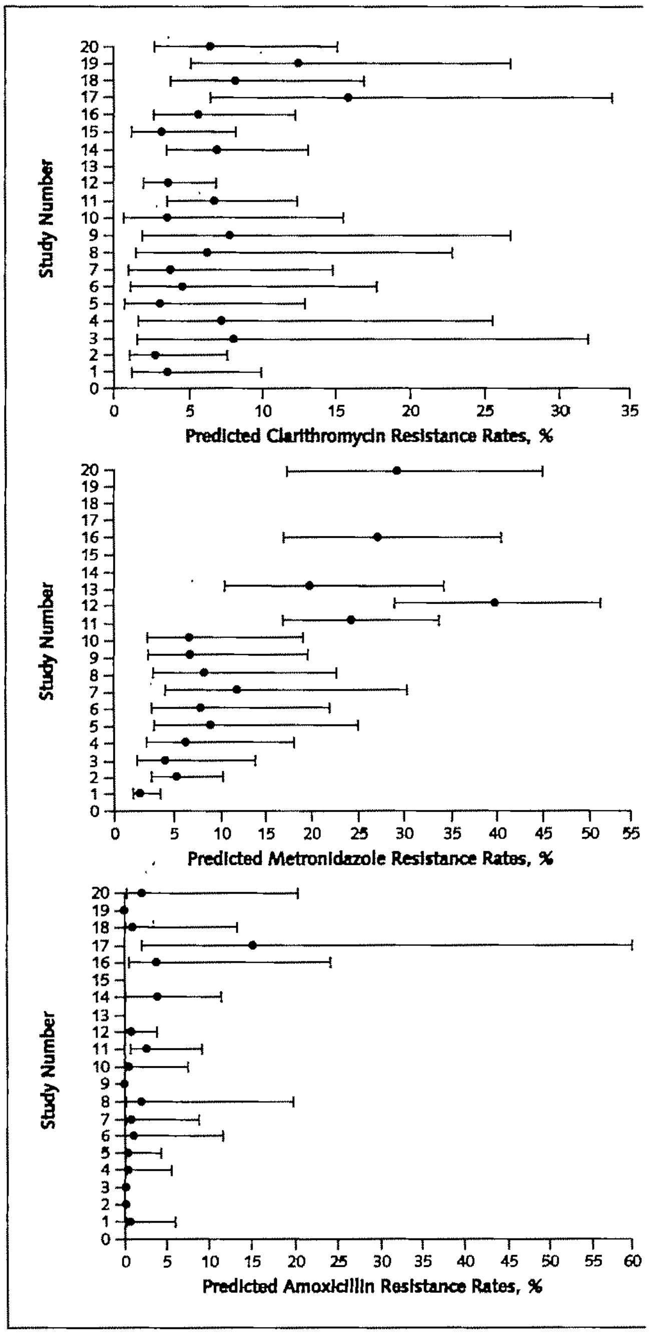
less precise in the multivariable model; therefore, relative risks were not calculated for amoxicillin.

In univariate analyses, significant differences in clarithromycin resistance were seen for the following risk factors: geographic region ($P = 0.014$), age ($P < 0.001$), sex ($P < 0.001$), year of enrollment ($P = 0.003$), ulcer status ($P < 0.001$), and study ($P = 0.004$). In the multivariable model, clarithromycin resistance varied significantly by geographic region and by study (**Table 3**). The highest resistance rates, 13.9% and 13.0%, occurred in the mid-Atlantic and northeastern regions of the United States, respectively. For the mid-Atlantic region, the relative risk was 3.1 (CI, 1.2 to 8.8) and the odds ratio was 3.4 (CI, 1.2 to 9.8). For the northeastern region, the relative risk was 3.4 (CI, 1.2 to 9.9) and the odds ratio was 3.7 (CI, 1.3 to 11.2). The Great Plains region seemed to influence regional differences in resistance rates, but region retained its significance when the Great Plains were excluded from the model. Clarithromycin resistance was also significantly more likely in older patients, women (relative risk, 1.6 [CI, 1.3 to 2.0]; odds ratio, 1.7 [CI, 1.4 to 2.2]), and patients with an inactive ulcer (relative risk, 1.9 [CI, 1.4 to 2.5]; odds ratio, 2.0 [CI, 1.5 to 2.8]).

In univariate analyses, metronidazole resistance was significantly associated with geographic region ($P = 0.042$), age ($P = 0.002$), sex ($P < 0.001$), ethnicity ($P < 0.001$), ulcer status ($P < 0.001$), test method ($P < 0.001$), and study ($P < 0.001$). Metronidazole resistance rates varied significantly among geographic regions; unadjusted rates ranged from 29.5% in the mid-Atlantic region to 40% in the southeastern United States. In the multivariable model, metronidazole resistance was significantly associated with female sex (relative risk, 1.7 [CI, 1.5 to 2.0]; odds ratio, 2.0 [CI, 1.9 to 2.8]), Asian ethnicity (relative risk, 1.9 [CI, 1.5 to 2.6]; odds ratio, 2.8 [CI, 1.8 to 4.5]), earlier year of enrollment, E-test use, and study. When we analyzed resistance rates by both age and sex, metronidazole resistance rates were highest (52% [CI, 45.6% to 58.2%]) in women younger than 40 years of age (132 of 254 patients). In comparison, metronidazole resistance was 47% (CI, 43.3% to 50.8% [330 of 701 patients]) in women at least 40 years of age, 32.4% (CI, 28.5% to 36.5% [179 of 553 patients]) in men younger than 40 years of age, and 30.7% (CI, 28.2% to 33.2% [423 of 1380 patients]) in men at least 40 years of age.

Year was a significant factor in the multivariable model for metronidazole; however, the rates were highly variable over time. Resistance was highest during the years when the E-test was used (1994–1996). Thirty-two percent (130 of 407 patients), 100% (623 of 623

Figure 1. **Predicted antimicrobial resistance rates by study.**



Error bars represent 95% CIs.

patients), and 67% (659 of 977 patients) of the data for 1994, 1995, and 1996, respectively, were derived from E-test results. Unadjusted resistance rates for metronidazole were 10.1% (28 of 277 patients) in 1994 and 42.1% (134 of 318 patients) in 1996 with agar dilution only and 43.1% (56 of 130 patients) in 1994, 51.2% (319 of 623 patients) in 1995, and 46.1% (304 of 659 patients) in 1996 with the E-test only. In 1995, no results were reported for agar dilution.

Amoxicillin resistance was low overall. In univariate analyses, resistance rates varied significantly only by study ($P = 0.002$). In the multivariable model, none of the covariates was significantly associated with amoxicillin resistance.

Simultaneous resistance to clarithromycin and metronidazole was also investigated. A total of 2832 isolates were tested for susceptibility to both clarithromycin and metronidazole, and 110 of 2832 (3.9% [CI, 3.2% to 4.7%]) had dual resistance. Multivariable analysis showed that resistance to both agents was significantly associated with sex ($P < 0.001$), age ($P = 0.001$), year ($P = 0.094$), ethnicity ($P = 0.03$), and study ($P = 0.069$). The dual-resistance rate was 6.9% in women (65 of 936 patients), 2.4% in men (45 of 1896 patients), 2.3% in patients younger than 40 years of age (18 of 794 patients), and 4.5% in patients at least 40 years of age (92 of 2038 patients). Dual-resistance rates increased from 0% (0 of 92 patients) in 1993 to 5.4% (50 of 932 patients) in 1996 and then decreased again to 2.1% (4 of 187 patients) in 1999. Asian persons had the highest rate of dual resistance (8.0% [8 of 100 patients]), while patients whose ethnicity was classified as "other" had the lowest rate of dual resistance (0.86% [1 of 116 patients]). Dual-resistance rates varied by study, from 0% (0 of 182 patients) to 6.9% (10 of 144 patients).

Utilization Data

During the 1990s, when rates of oral macrolide and metronidazole use were relatively stable, clarithromycin resistance rates were stable and metronidazole resistance rates varied (**Figure 2**). The slight downward trend in purchase of macrolide units between 1995 and 1998 was driven by the decreasing use of erythromycin. Use of the newer macrolides, clarithromycin and azithromycin, which require less frequent dosing and fewer tablets per treatment course, remained constant or increased over the same time period, respectively.

DISCUSSION

Pretreatment antimicrobial resistance of *H. pylori* has been found to have a negative impact on treatment

Table 2. **In Vitro Susceptibility of *Helicobacter pylori* Isolates Collected between 1993 and 1999***

Agent	Patients†	MIC_{50}	MIC_{90}	Range	Susceptible Isolates	Intermediate Isolates	Resistant Isolates
	n	←	μg/mL	→	←	%	→
Clarithromycin	3571	0.03	1.0	0.004 to >256	89.2	0.7	10.1
Agar dilution	2152	0.03	2.0	0.004 to >256	89.3	0.2	10.6
E-test	1419	0.03	0.38	0.016 to >256	89.1	1.6	9.4
Metronidazole	2883	4	>32	≤0.002 to >256	57.7	5.4	36.9
Agar dilution	1471	2	64	0.012 to >256	68.0	5.9	26.1
E-test	1412	16	>32	≤0.002 to >256	46.9	5.0	48.1
Amoxicillin	3486	≤0.016	0.06	<0.016 to >256	98.6	–	1.4
Agar dilution	2070	0.016	0.06	<0.016 to [illegible]6	98.9	–	1.1
E-test	1416	≤0.016	0.06	<0.016 to >256	98.2	–	1.8

* MIC = minimal inhibitory concentration. Breakpoints used to define susceptible, intermediate, and resistant categories are as follows. Clarithromycin: ≤0.25 μg/mL = susceptible, >0.25 to <1 μg/mL = intermediate, ≥1 μg/mL = resistant; metronidazole: ≤8 μg/mL = susceptible, >8 to <32 μg/mL = intermediate, ≥32 μg/mL = resistant; amoxicillin: ≤0.25 μg/mL = susceptible, >0.25 μg/mL = resistant.

† In 106 patients, susceptibility testing for all three drugs was performed by both E-test and agar dilution. Only the results from agar dilution were included.

efficacy (22, 23). Clarithromycin resistance seems to be the most compromising factor. Resistance reduces treatment efficacy by an average of 55.4% (CI, 33.2% to 77.6%), as determined by meta-analytic methods (24). However, all regimens may not be equally affected. Data from FDA-approved regimens show that resistance has the greatest effect on dual therapy with clarithromycin and an antisecretory agent; such therapy fails in 95.1% of patients (39 of 41) with resistant pretreatment isolates (7). Although triple-drug therapies are less affected, they also fail in 68.6% of patients (24 of 35) with resistant pretreatment isolates (7).

Pretreatment resistance to metronidazole does not always predict decreased clinical efficacy (25) and is complicated by the lack of a standard in vitro method for determining susceptibility. However, two recent meta-analyses showed that pretreatment metronidazole resistance predicts poor outcome after treatment with a metronidazole-containing regimen (24, 26). In one analysis, which examined all metronidazole-containing regimens (24), resistance was found to reduce effectiveness by an average of 37.7% (CI, 29.6% to 45.7%). In the second analysis (26), nitroimidazole-containing triple-therapy regimens achieved 90% eradication in patients with susceptible strains but less than 75% eradication in patients with resistant strains. Only quadruple-therapy regimens (a proton-pump inhibitor, bismuth, tetracycline, and metronidazole) given for at least 1 week were equally effective in treating metronidazole-susceptible and metronidazole-resistant strains (92% [range, 63% to 100%]).

Amoxicillin resistance is rare but has been associated with a reduction in the efficacy of dual therapy with omeprazole and amoxicillin (27). The clinical relevance of amoxicillin resistance in triple-therapy regimens has not been studied.

The NCCLS has only recently standardized methods, including medium, inoculum, and incubation, for testing the susceptibility of *H. pylori* to clarithromycin. Agar dilution is the preferred method (5). Testing conditions, including choice of medium, age of the colonies, incubation period and conditions, and inoculum size, have been shown to influence results of tests for susceptibility to metronidazole (28, 29). It is recognized that E-test results for metronidazole do not always correlate with those of agar dilution (6, 30). In the United States, the overall rate of metronidazole resistance was found to be 39% (690 of 1768 isolates) by E-test and 25.7% (317 of 1234 isolates) by the NCCLS agar dilution method (30). Data gathered in Europe from a large multinational, multicenter randomized clinical trial showed that 36% of isolates (171 of 469) were resistant to metronidazole on E-test and 29% (136 of 469) were resistant on agar dilution; the criterion for resistance was an MIC value greater than 8 μg/mL. Of the 333 isolates classified as susceptible to metronidazole on agar dilution, 72 (22%) were resistant on the E-test (6). Conversely, MIC results obtained for clarithromycin seemed to be similar for both methods (6, 31). E-test MIC values for amoxicillin have been reported to be within one- to twofold of MIC values on agar dilution (31). In our

Table 3. **Factors Associated with *Helicobacter pylori* Resistance***

Factor	Clarithromycin					Metronidazole	
	Unadjusted Resistance Rate	Predicted Resistance Rate (95% CI)	Predicted RR (95% CI)	Adjusted OR (95% CI)	*P* Value†	Unadjusted Resistance Rate	Predicted Resistance Rate (95% CI)
	% (n/n)	%				*% (n/n)*	%
Geographic region					0.050		
Northeast	13.0 (32/246)	11.5 (5.9–21.3)	3.4 (1.2–9.9)	3.7 (1.3–11.2)		31.2 (57/183)	19.4 (12.2–29.4)
Mid-Atlantic	13.9 (60/432)	10.6 (5.7–18.9)	3.1 (1.2–8.8)	3.4 (1.2–9.8)		29.5 (105/356)	20.2 (13.4–29.2)
Southeast	10.4 (72/691)	8.5 (4.5–15.5)	2.5 (0.9–6.9)	2.7 (0.9–7.7)		40.0 (221/553)	24.9 (17.2–34.5)
Central	8.5 (26/305)	7.3 (3.6–14.2)	2.2 (0.8–6.3)	2.3 (0.8–6.8)		37.7 (92/244)	22.1 (14.6–32.0)
Midwest	11.9 (39/327)	9.3 (4.7–17.5)	2.7 (1.0–7.8)	2.9 (1.0–8.6)		37.8 (104/275)	21.7 (14.2–31.7)
South	9.0 (50/558)	7.0 (3.6–13.2)	2.1 (0.8–5.8)	2.2 (0.7–6.2)		38.3 (174/454)	22.0 (14.9–31.3)
Great Plains	4.1 (4/97)	3.4 (1.0–10.4)	1.0 (referent)	1.0 (referent)		37.0 (37/100)	22.5 (13.4–35.2)
Northwest	10.0 (12/120)	8.3 (3.7–17.8)	2.4 (0.8–7.8)	2.6 (0.8–8.5)		32.1 (34/106)	16.6 (9.8–26.6)
Southwest	8.2 (65/795)	6.7 (3.5–12.4)	2.0 (0.8–5.5)	2.1 (0.7–5.9)		39.1 (239/612)	24.3 (16.9–33.8)
Age‡			1.2 (1.1–1.3)	1.2 (1.1–1.3)	<0.001		
<40 y	7.5 (77/1030)	5.5 (2.8–10.4)				38.5 (311/807)	25.7 (17.7–35.7)
40–65 y	10.5 (222/2107)	6.7 (3.5–12.4)				37.7 (648/1721)	24.3 (16.9–33.8)
>65 y	14.1 (61/434)	9.3 (4.8–17.0)				29.3 (104/355)	22.1 (15.0–31.4)
Sex					<0.001		
Female	13.5 (165/1223)	10.9 (5.8–19.7)	1.6 (1.3–2.0)	1.7 (1.4–2.2)		48.3 (461/954)	42.4 (31.4–54.2)
Male	8.3 (195/2348)	6.7 (3.5–12.4)	1.0 (referent)	1.0 (referent)		31.2 (602/1929)	24.3 (16.9–33.8)
Year§			0.9 (0.7–1.3)	1.0 (0.7–1.3)	>0.2		
1993	4.3 (4/92)	7.6 (2.4–21.7)				8.7 (8/92)	40.9 (22.4–62.4)
1994	7.8 (32/409)	7.3 (2.9–17.0)				20.6 (84/407)	35.3 (21.7–51.9)
1995	8.8 (55/625)	7.0 (3.4–13.8)				51.2 (319/623)	29.7 (20.0–41.6)
1996	10.2 (95/935)	6.7 (3.5–12.4)				44.8 (438/977)	24.3 (16.9–33.8)
1997	10.4 (22/212)	6.3 (3.0–12.8)				25.0 (2/8)	19.6 (12.5–29.3)
1998	12.0 (131/1090)	6.0 (2.3–14.5)				28.2 (166/589)	15.5 (8.3–26.9)
1999	10.1 (21/208)	5.6 (1.7–17.2)				24.6 (46/187)	12.1 (5.3–25.4)
Ethnicity					>0.2		
Asian	11.0 (13/118)	8.1 (3.5–17.5)	1.2 (0.7–2.1)	1.2 (0.8–2.1)		55.4 (56/101)	46.8 (32.4–61.8)
Black	9.3 (77/829)	5.8 (2.9–11.3)	0.9 (0.7–1.1)	0.9 (0.7–1.1)		44.6 (300/672)	37.8 (27.2–49.7)
Hispanic	8.5 (28/331)	6.8 (3.4–13.1)	1.0 (0.7–1.6)	1.0 (0.7–1.5)		43.2 (142/329)	34.9 (25.0–46.3)
White	10.8 (223/2066)	6.7 (3.5–12.4)	1.0 (referent)	1.0 (referent)		30.8 (512/1665)	24.3 (16.9–33.8)
Other	8.4 (19/227)	6.2 (2.7–13.5)	0.9 (0.6–1.6)	0.9 (0.6–1.5)		45.7 (53/116)	38.1 (25.2–52.9)
Ulcer status					<0.001		
Active ulcer	8.6 (232/2683)	6.7 (3.5–12.4)	1.0 (referent)	1.0 (referent)		34.6 (729/2105)	24.3 (16.9–33.8)
Inactive ulcer	14.4 (128/887)	12.6 (6.5–22.9)	1.9 (1.4–2.5)	2.0 (1.5–2.8)		43.0 (334/777)	22.7 (14.9–33.0)
Test method					>0.2		
Agar	10.5 (227/2152)	6.7 (3.5–12.4)	1.0 (referent)	1.0 (referent)		26.1 (384/1471)	24.3 (16.9–33.8)
E-test	9.4 (133/1419)	6.6 (1.9–20.3)	1.0 (0.3–3.4)	1.0 (0.5–2.0)		48.1 (679/1412)	61.6 (37.1–81.3)
Study‖	4.7 (6/129) to 24.0 (12/50)¶	2.8 (1.0–7.6) to 15.8 (6.5–33.6)**	–	–	0.010	4.4 (8/182) to 54.3 (121/223)††	1.3 (0.5–3.5) to 39.7 (29.0–51.4)‡‡

* OR = odds ratio; RR = relative risk.
† From the full multivariable logistic regression model.
‡ Odds ratios for age were calculated per decade of life.
§ Odds ratios for year were calculated per year of enrollment.
‖ Values are ranges for groups of studies.
¶ Study 10 to study 17.
** Study 2 to study 17.
†† Study 1 to study 17.
‡‡ Study 1 to study 12.
§§ Study 7 to study 2.
‖‖ Study 5 to study 17.

analysis, results for clarithromycin resistance were similar on agar dilution and the E-test. However, metronidazole resistance was 22% higher with the E-test than with agar dilution. Although resistance rates for amoxicillin differed slightly between the two testing methods, the difference is probably not clinically relevant since the overall rate of amoxicillin resistance is low.

In the multivariable analysis, geographic region was found to be significantly associated with clarithromycin resistance. Resistance rates were highest on the East

Table 3—**Continued**

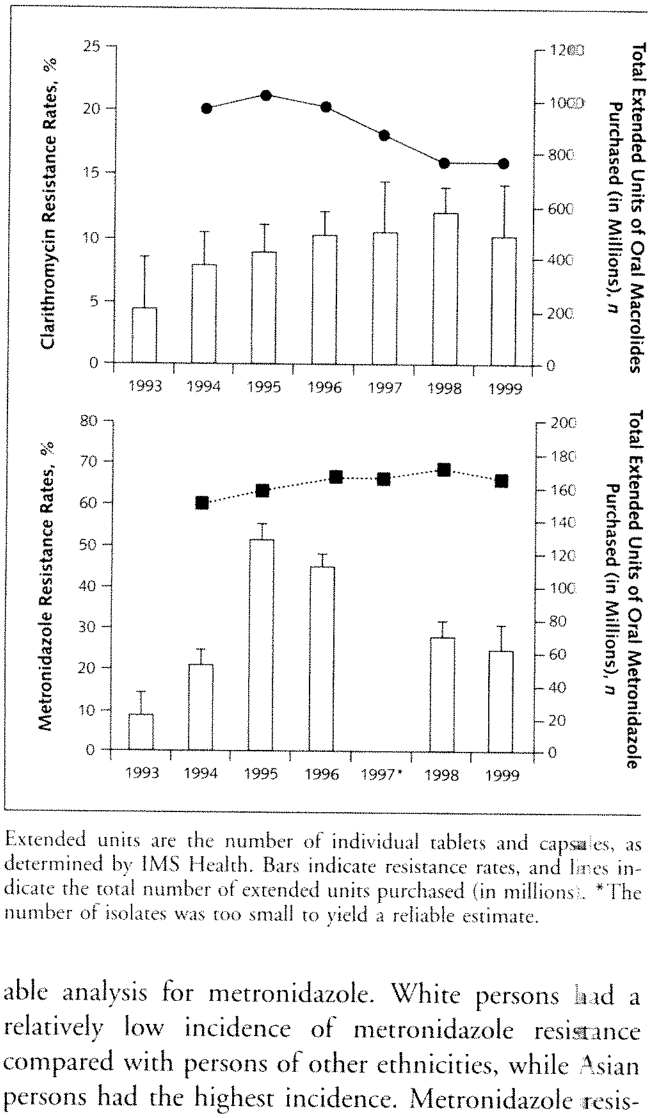
Metronidazole			Amoxicillin			
Predicted RR (95% CI)	**Adjusted OR (95% CI)**	***P* Value†**	**Unadjusted Resistance Rate**	**Predicted Resistance Rate (95% CI)**	**Adjusted OR (95% CI)**	***P* Value†**
			% (n/n)	%		
		>0.2				>0.2
1.0 (0.7–1.4)	1.0 (0.6–1.5)		0 (0/237)	–	–	
1.0 (referent)	1.0 (referent)		1.9 (8/422)	2.7 (0.7–10.2)	–	
1.2 (1.0–1.6)	1.3 (1.0–1.8)		0.9 (6/670)	1.5 (0.3–6.0)	–	
1.1 (0.8–1.5)	1.1 (0.8–1.7)		2.0 (6/296)	3.2 (0.8–11.9)	–	
1.1 (0.8–1.4)	1.1 (0.8–1.6)		2.2 (7/320)	3.8 (0.9–15.0)	–	
1.1 (0.8–1.4)	1.1 (0.8–1.6)		1.1 (6/553)	1.5 (0.3–6.1)	–	
1.1 (0.8–1.7)	1.2 (0.7–1.9)		2.1 (2/97)	3.6 (0.5–19.9)	–	
0.8 (0.5–1.2)	0.8 (0.5–1.3)		2.7 (3/113)	4.3 (0.9–18.7)	–	
1.2 (0.9–1.6)	1.3 (0.9–1.8)		1.3 (10/778)	2.5 (0.7–9.0)	–	
1.0 (0.9–1.0)	0.9 (0.9–1.0)	0.084			1.0 (0.8–1.2)	>0.2
			1.4 (14/1011)	2.6 (0.7–9.8)		
			1.4 (29/2063)	2.5 (0.7–9.0)		
			1.2 (5/412)	2.3 (0.6–8.7)		
		<0.001				>0.2
1.7 (1.5–2.0)	2.0 (1.9–2.8)		1.6 (19/1177)	3.1 (0.8–11.5)	1.5 (1.4–1.7)	
1.0 (referent)	1.0 (referent)		1.3 (29/2309)	2.5 (0.7–9.0)	1.0 (referent)	
0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.036			0.5 (0.2–1.2)	0.128
			3.3 (3/92)	13.2 (1.1–68.2)		
			1.0 (4/407)	8.5 (1.1–43.5)		
			1.8 (11/624)	4.7 (1.0–19.6)		
			1.9 (18/937)	2.5 (0.7–9.0)		
			0.6 (1/155)	1.3 (0.2–6.2)		
			1.0 (11/1063)	0.6 (0.1–5.8)		
			0 (0/208)	0.3 (0–6.2)		
		<0.001				>0.2
1.9 (1.5–2.6)	2.8 (1.8–4.5)		1.7 (2/118)	2.4 (0.4–14.0)	1.0 (0.3–3.7)	
1.6 (1.3–1.8)	1.9 (1.5–2.4)		2.1 (17/822)	4.1 (1.0–15.3)	1.9 (0.9–3.9)	
1.4 (1.2–1.8)	1.7 (1.3–2.3)		0.9 (3/332)	1.8 (0.4–8.5)	0.8 (0.3–2.4)	
1.0 (referent)	1.0 (referent)		1.2 (25/2013)	2.5 (0.7–9.0)	1.0 (referent)	
1.6 (1.2–2.1)	2.0 (1.3–3.1)		0.5 (1/201)	1.3 (0.1–12.8)	0.6 (0.1–3.2)	
		>0.2				>0.2
1.0 (referent)	1.0 (referent)		1.2 (32/2670)	2.5 (0.7–9.0)	1.0 (referent)	
0.9 (0.8–1.2)	0.9 (0.7–1.2)		2.0 (16/815)	3.5 (0.8–14.0)	1.2 (0.8–1.8)	
		0.002				>0.2
1.0 (referent)	1.0 (referent)		1.1 (22/2070)	2.5 (0.7–9.0)	1.0 (referent)	
2.5 (1.5–4.1)	5.0 (1.7–14.4)		1.8 (26/1416)	4.2 (0.5–28.0)	1.4 (0.4–4.4)	
–	–	<0.001	0 (0/187) to 6.0 (3/50)§§	0.2 (0–4.2) to 15.2 (2.1–59.7)‖‖	–	0.200

Coast (mid-Atlantic and northeast regions). It is not known why clarithromycin resistance rates differ by region. Prescribing trends for oral macrolides may have an effect, but macrolide utilization data were not available by geographic region.

Older age was shown to be significantly associated with clarithromycin resistance. Younger age seemed to be associated with metronidazole resistance on multivariable analyses, although the association was not significant. These trends may be explained by the general usage patterns for these classes of antimicrobials. Elderly patients are more likely to have respiratory tract infections, for which macrolides are commonly prescribed, and young women with gynecologic infections are likely to be treated with metronidazole. Metronidazole resistance in European countries has been found to be highest (50%) in young women 20 to 39 years of age (28). In our study, female sex was significantly associated with resistance to both metronidazole and clarithromycin in the multivariable analyses. Women younger than 40 years of age had the highest rates of metronidazole resistance. It is not clear, however, why women are more likely to be resistant to clarithromycin.

Ethnicity was a significant factor in the multivari-

Figure 2. **Antimicrobial resistances rates in the United States in relation to the total number of extended units purchased.**



Extended units are the number of individual tablets and capsules, as determined by IMS Health. Bars indicate resistance rates, and lines indicate the total number of extended units purchased (in millions). *The number of isolates was too small to yield a reliable estimate.

able analysis for metronidazole. White persons had a relatively low incidence of metronidazole resistance compared with persons of other ethnicities, while Asian persons had the highest incidence. Metronidazole resistance has previously been linked to ethnic origin and nationality. In an analysis of data from 11 European countries, rates of resistance to metronidazole were higher in nonwhite patients from northern Africa and from Mediterranean countries than in patients from northern European countries (28). The reason for this is unclear.

In the multivariable analysis, patients with an inactive ulcer had significantly higher antimicrobial resistance rates for clarithromycin than those who had active ulcer disease. Our database did not contain information on previous antimicrobial therapy. Recent past use of antimicrobials (range, 2 to 8 weeks) was an exclusion criterion for all of the 20 included trials, and we were unable to determine the impact of antimicrobial use in the distant past on *H. pylori* resistance. Patients with inactive ulcer disease may have been exposed to previous unsuccessful therapies for *H. pylori* eradication; this may explain the higher rates of clarithromycin resistance in this population. However, of the 20 included trials, 17 noted previous eradication therapy as an exclusion criterion. Two trials excluded patients who had received previous treatment for *H. pylori* at any time, and 12 trials excluded patients who had recently received treatment for *H. pylori* (within 4 weeks to 1 year before enrollment). One trial specifically excluded patients who were previously treated with a metronidazole-containing regimen, and 2 trials excluded those previously treated with a macrolide-containing regimen. Despite these exclusion criteria, higher resistance rates in patients with inactive ulcer disease suggest that the prescriber should ask patients about previous antimicrobial use, especially macrolides, before selecting a treatment regimen.

Year of enrollment was not significantly associated with resistance for any of the three agents. While clarithromycin and amoxicillin resistance seemed stable between 1993 and 1999 in the multivariable analyses, metronidazole resistance tended to decrease. Although metronidazole resistance rates decreased over time, resistance was highest during the years when E-testing was used (1994–1996). Therefore, the observed changes in metronidazole resistance may not represent true changes in susceptibility in the population but may instead represent changes in in vitro testing methods over time. Resistance to metronidazole has been reported to be relatively constant in Belgium and Japan, with only a slight increase in recent years in Belgium (32, 33). Amoxicillin resistance was low overall in our analysis, so although the rates decreased over time, this finding has little clinical significance. Resistance of *H. pylori* to clarithromycin has been tracked in Belgium since 1990 and has been relatively stable overall, with a peak of 13.2% in 1997 (32). In contrast, in two regions of Japan, the prevalence of clarithromycin resistance doubled from 9.1% in 1996 to 18.7% during 1998 and 1999 (33).

To further evaluate trends of clarithromycin and metronidazole resistance over time in our population, we analyzed IMS Health data, which track antimicrobial utilization. In the setting of relatively stable rates of overall use of oral macrolide and metronidazole antimicrobials between 1994 and 1999, *H. pylori* had stable rates of resistance to clarithromycin and variable rates of resistance to metronidazole. In addition, rates of metronidazole resistance decreased slightly between 1995 and 1999. It should be noted that these data reflect drug use in the general population and include children and persons not infected with *H. pylori*. Data on antimicrobial use for populations similar to those included in our study are not available. Even in prospective studies that ask about past antimicrobial use, this information might not be reliably collected. Nevertheless, it will be interesting to follow antimicrobial utilization in the future as macrolides are used more frequently to treat a variety of infections.

Surveillance data obtained from our large database are helpful in understanding the risk factors that predict antimicrobial resistance patterns. However, a clinical trial database does not represent a random sample of the general population, and extrapolation to general medical practice should be done cautiously. In addition, despite our efforts to control for confounding due to study differences, the possibility that the reported resistance rates may be distorted by residual confounding cannot be completely excluded. We have presented predicted antimicrobial resistance rates, in addition to the unadjusted rates, to control for confounding. We have also included both relative risks and odds ratios to characterize any disparity that might occur as resistance rates increase. However, readers should not try to generalize results for the predicted resistance rates and relative risks. Covariate patterns that differ from those of the "average" patient, as defined in our model, can produce different results.

Susceptibility information on *H. pylori* should continue to be collected to allow researchers to follow trends in antimicrobial resistance and better understand the significance of the identified risk factors. Such information will be helpful in the selection of empirical antimicrobial agents for treatment of *H. pylori* infection and may encourage the use of culture and susceptibility testing in patients at risk for resistant organisms. More detailed utilization data are needed to evaluate the effect of drug utilization on resistance over time.

In conclusion, we have identified several risk factors associated with pretreatment antimicrobial resistance. Pretreatment resistance to clarithromycin and metronidazole has a significant negative impact on treatment efficacy. In addition, these agents are of great importance in standard treatment regimens. Therefore, clinicians should consider these risk factors when deciding which patients should have susceptibility testing and when choosing appropriate *H. pylori* treatment regimens in the empirical setting.

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Recovery Rate and Prognosis in Older Persons Who Develop Acute Lung Injury and the Acute Respiratory Distress Syndrome

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Background: The incidence of acute respiratory failure requiring mechanical ventilation increases 10-fold from the ages of 55 to 85 years, yet the rate of recovery and outcomes in older persons who develop acute lung injury are poorly defined.

Objective: To examine age as an independent risk factor in recovery and intensive care unit discharge after acute lung injury.

Design: Prospective cohort study.

Setting: 10 U.S. university-based medical centers.

Patients: 902 mechanically ventilated patients enrolled in randomized, controlled trials for the treatment of acute lung injury. All patients were managed according to a standardized protocol for ventilator management and weaning.

Measurements: Frequency and time to achieve well-defined recovery landmarks, duration of ventilation and intensive care unit stay, and survival.

Results: Median duration of mechanical ventilation was 19 days (interquartile range, 7 to >28 days) for patients 70 years of age or older ($n = 173$) compared with 10 days (interquartile range, 5 to 26 days) for patients younger than 70 years of age ($n = 729$) ($P < 0.001$). The duration of intensive care unit stay was 21 days for the older group (interquartile range, 11 to >28 days) and 16 days for the younger group (8 to >28 days) ($P = 0.004$). Survival rates decreased across increasing decades of age ($P < 0.001$): Patients younger than 70 years of age had a greater 28-day survival rate than patients 70 years of age or older (74.6% vs. 50.3%; $P < 0.001$). The proportion of survivors achieving physiologic recovery landmarks did not differ between the older and younger age groups, and the median time to pass a 2-hour spontaneous breathing trial was similar between both the older and younger patients (4 days vs. 5 days; $P > 0.2$). After passing a spontaneous breathing trial, however, older patients required 1 more day than younger patients to achieve unassisted breathing ($P = 0.002$) and 3 more days to leave the intensive care unit ($P = 0.005$). In a multivariable Cox proportional hazards analysis, age of 70 years or older was a strong predictor of in-hospital death (hazard ratio, 2.5 [95% CI, 2.0 to 3.2]; $P < 0.001$).

Conclusions: Although the survival rate among patients 70 years of age or older was high, these patients were twice as likely to die of acute lung injury compared with their younger counterparts, even after adjustment for covariates. Older survivors recovered from respiratory failure and achieved spontaneous breathing at the same rate as younger patients but had greater difficulty achieving liberation from the ventilator and being discharged from the intensive care unit.

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More than half of all days spent in an intensive care unit are incurred by patients older than 65 years of age, and the number of days per year spent in the intensive care unit (per 1000 person-years) is sevenfold higher for persons older than 75 years compared with persons younger than 65 years (1). The population of older persons and their respective proportion of health care expenditures are expected to double by 2030 (2), and some have suggested that we ration the care provided to older patients (3–5). Indeed, physicians in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) withheld mechanical ventilation at higher rates in older patients, especially in patients 70 years of age or older (6–8). However, previous reports of older patients with respiratory failure from various causes have indicated that recovery and overall prognosis in this age group do not justify using age alone to determine treatment decisions (9–11). Instead, the decision to place older persons with acute lung injury on mechanical ventilation should incorporate several factors, including comorbid illnesses (12), patient preference or previously stated wishes, physician gestalt, and bedside judgment.

The incidence of acute respiratory failure requiring mechanical ventilation increases 10-fold from the ages of 55 to 85 years (13), resulting in an increasing number of elderly patients receiving treatment in intensive care units (1, 11, 14). Therefore, health care professionals need to understand the effect of age on outcomes of acute lung injury and the acute respiratory distress syndrome (henceforth called acute lung injury) to guide their treatment decisions and prognostic discussions (15, 16).

In most investigations, the mortality rate from acute lung injury has ranged from 40% to 50% (15, 17–21).

Data from a large cohort followed from 1983 to 1993 revealed encouraging declines in acute lung injury–related mortality but showed that these improved outcomes were confined largely to patients younger than 60 years of age (22). We used data from an acute lung injury database sponsored by the National Heart, Lung, and Blood Institute (23, 24) to investigate the effect of age on the ability to recover from acute lung injury—information that could prove extremely important given the growing number of older persons at risk for acute lung injury (2–5, 16, 25).

We hypothesized that age would independently affect acute lung injury outcomes, even after adjustment for severity of illness and other covariates. To investigate this hypothesis, we asked the following questions about age and acute lung injury: 1) How does age affect survival from acute lung injury? 2) Do physiologic recovery and successful liberation from the ventilator take longer in older patients?

METHODS

Patients

We examined data on 902 patients who participated in the National Heart, Lung, and Blood Institute multicenter, randomized trials of the Acute Respiratory Distress Syndrome (ARDS) Network between 18 March 1996 and 28 May 1999. Patients were enrolled from 24 hospitals associated with 10 U.S. medical centers. Included in this analysis were the 861 patients from a recently reported randomized trial of mechanical ventilation that compared lower with traditional tidal volume (6 mL/kg of ideal body weight vs. 12 mL/kg of ideal body weight) (24). After the early stopping of the ventilator trial by the data safety monitoring board for efficacy, the 41 additional patients in our analysis had received lisofylline or placebo with the lower tidal-volume strategy. (Lisofylline is a xanthine derivative that decreases the inflammatory response.) The institutional review boards of each participating medical center or hospital approved this study. Patients or their surrogate provided informed consent before enrollment. The study was conducted in accordance with the established ethical standards of the medical centers and with the principles of the Declaration of Helsinki (26).

We analyzed age as a binary category and according to decade. To assess the varying effect of age on outcomes, we also used age, coded as a series of indicator variables for decade of age, in multivariable analysis. In keeping with our prospectively defined analysis plan, we decided a priori to report these data as a comparison of the patients younger than 70 years of age ($n = 729$) with the patients 70 years of age or older ($n = 173$). In the absence of any clearly defined age cutoff designating patients as elderly, we chose these binary age categories on the basis of data from the SUPPORT studies suggesting that physicians most often used 70 to 75 years of age as a decision-making cut point affecting intensity of care and threshold for withholding mechanical ventilation (6–8). However, additional analyses defining "older persons" at lower (65 years of age) and higher (80 years of age) cutoffs have yielded similar results.

Details of inclusion and exclusion criteria for the ARDS network trials have been reported previously (23, 24). Briefly, patients were eligible if they required mechanical ventilation for acute lung injury, with a partial P_{O_2} divided by fraction of inspired oxygen of 300 or less, bilateral pulmonary infiltrates consistent with pulmonary edema, and no clinical evidence of left atrial hypertension. If measured, the pulmonary capillary wedge pressure was required to be 18 mm Hg or less (27). The major reasons for exclusion were as follows: more than 36 hours elapsed since the inclusion criteria were met, age younger than 18 years, participation in other acute lung injury trials in the past 30 days, pregnancy, increased intracranial pressure, neuromuscular disease that could impair spontaneous breathing, sickle-cell disease, severe chronic respiratory disease (as previously described [23, 24]), massive obesity, burns covering more than 30% of body surface, comorbid conditions with an estimated 6-month mortality rate greater than 50%, bone marrow or lung transplantation, chronic liver disease (as defined by Child–Pugh Class C [28]), inability to consent, and attending physician refusal or unwillingness to commit full life support. The patient's surrogate and managing physician determined whether to withdraw mechanical ventilation, and we analyzed all patient data on an intention-to-treat basis.

Protocol for Mechanical Ventilator Management

Mechanical ventilation was performed in strict accordance with the ARDS network study protocol (24). Weaning was done according to a protocol that included a daily weaning screen followed by pressure support ventilation and a 2-hour spontaneous breathing trial.

The Daily Weaning Screen and Spontaneous Breathing Trials

Patients were followed daily to determine when they passed the following "weaning screens," which were based on data from previous investigations (29–31): oxygen saturation of at least 0.88 on positive end-expiratory pressure of 8 cm H_2O or less and a fraction of inspired oxygen of 0.40 or less, systolic blood pressure of 90 mm Hg or more without vasopressor support, and demonstration of spontaneous inspiratory efforts (initiating breaths above the rate of the ventilator setting). After meeting these daily weaning screen criteria, patients were given a 5-minute trial of spontaneous breathing with continuous positive airway pressure of 5 cm H_2O. If the respiratory rate remained 35 breaths/min or less, the patient entered a pressure support weaning protocol and then a 2-hour spontaneous breathing trial on a T-piece or continuous positive airway pressure of 5 cm H_2O without pressure support ventilation, as described previously (www.ardsnet.org/study.html). The spontaneous breathing trial was terminated if any of the following predetermined conditions were met: respiratory rate greater than 35 breaths/min for more than 5 minutes, sustained arterial oxygen saturation less than 0.90, heart rate that had increased by 20% or more compared with the rate at 0600 hours (6 a.m.), marked use of accessory respiratory muscles, abdominal paradox, marked subjective dyspnea, or diaphoresis. If any of these criteria were met, then the ventilator was set at the patient's previously used settings and the patient was weaned by using the pressure-support protocol until the following day, at which time the daily weaning screen would be performed again. Patients "passed" the spontaneous breathing trial if none of the above conditions were met. After passing the 2-hour spontaneous breathing trial, patients graduated to unassisted breathing, meaning that they were extubated, continued receiving a T-piece, or received continuous positive airway pressure of 5 cm water without pressure support ventilation.

Definitions of Recovery Landmarks

To determine the rate of recovery of older compared with younger patients, the earliest time at which patients had successfully passed four clearly defined recovery landmarks was recorded: 1) the daily weaning screen, 2) the 2-hour spontaneous breathing trial, 3) the date on which the patient began a period of unassisted breathing that lasted 48 hours or more, and 4) discharge from the intensive care unit alive and with no mechanical ventilation.

Severity of Illness Classification and Organ or System Failure

Baseline severity of illness was recorded at enrollment by using the Acute Physiology, Age, and Chronic Health Evaluation III (APACHE III) score (32). During analysis, we used a modified APACHE III score that excluded age so that age would remain an independent factor of outcome. Nonpulmonary organ system failures were also recorded by using definitions based on the following objective criteria (24, 33–35): for circulatory failure, a systolic blood pressure of 90 mm Hg or less or the need for treatment with any vasopressor; for coagulation failure, a platelet count of 80×10^9 cells/L or less; for central nervous system failure, a Glasgow coma scale rating less than 12; for hepatic failure, a serum bilirubin concentration of at least 34 μmol/L (2 mg/dL); and for renal failure, a serum creatinine concentration of at least 177 μmol/L (2 mg/dL).

Outcomes

Patients were assessed for duration of mechanical ventilation and total length of stay in the intensive care unit. To quantitate the degree and rate of recovery, we used the maximum recovery landmark achieved by day 28 in both survivors and nonsurvivors (and the time it took to progress through these landmarks). Patients were monitored daily for 28 days for signs of failure in nonpulmonary organs and systems. We calculated the number of days without organ or system failure (organ failure–free days) by subtracting the number of days with organ failure from the lesser of 28 days or the number of days to death.

Statistical Analysis

All univariate comparisons of older versus younger patients used the Fisher exact test for dichotomous variables (36), two-sided Wilcoxon test for noncensored continuous variables (37), and a log-rank test for censored continuous variables (38). Patients were followed

Table 1. **Baseline Characteristics of the Patients**

Characteristic	Patients < 70 Years of Age (n = 729)	Patients ≥ 70 Years of Age (n = 173)
Median age (interquartile range), *y*	46 (35–57)	75 (73–79)
Male sex, *n (%)*	431 (59.1)	166 (61.3)
Ethnicity, *n (%)*		
White, non-Hispanic	524 (71.9)	137 (79.2)
Black, non-Hispanic	133 (18.2)	22 (12.7)
Hispanic, Asian, or Native American	72 (9.9)	14 (8.1)
Median APACHE III score (interquartile range)*	73 (56–95)	73 (58–91)
Radiographic lung injury, *n (%)*†		
1 quadrant	2 (0.3)	2 (1.2)
2 quadrants	41 (5.7)	11 (6.5)
3 quadrants	128 (17.8)	26 (15.4)
4 quadrants	547 (76.2)	130 (76.9)
Nonpulmonary organ failure, *n (%)*‡		
0 organs	151 (20.7)	28 (16.2)
1 organ	338 (46.4)	85 (49.1)
2 organs	175 (24.0)	53 (30.6)
3 organs	54 (7.4)	5 (2.9)
4 organs	10 (1.4)	2 (1.2)
Primary causes of lung injury, *n (%)*§		
Pneumonia	267 (36.6)	53 (30.6)
Aspiration	95 (13.0)	39 (22.5)
Trauma	87 (11.9)	9 (5.2)
Sepsis	192 (26.3)	44 (25.4)
Multiple transfusions	15 (2.1)	11 (6.4)
Other	95 (13.0)	24 (13.9)

* Acute Physiology, Age, and Chronic Health Evaluation (32). Scores for these analyses were modified by excluding age. Higher scores indicate more-severe illness.

† Radiographic lung injury class based on number of quadrants opacified on portable chest radiography.

‡ Organ and system failures were defined as described previously (24, 33–35).

§ The sum of all primary causes of lung injury is greater than 100% because the investigators assigned more than one cause for some lung injuries.

until discharge home or for 180 days, whichever occurred first. We compared the mortality rates at 28 and 180 days by using Kaplan–Meier estimates and their standard errors (38) at this time point, with stratification on treatment assignment. Association of mortality and age decade was quantified and tested by using the Spearman rank correlation coefficient (39). A priori, we determined the covariates to use in multivariable regressions: study center, sex, race/ethnicity, cause of acute lung injury, modified APACHE III score (32) and its square (linear variables), organ systems failure index (a linear variable) (33), radiographic lung injury score (a linear variable), and treatment assignment. Organ system failure–free days (counted separately for each organ system) were stratified on day of death in the first 28 days or on survival after day 28. Data on organ failure were not available beyond the day 28. Within each stratum, we determined fractional ranks of organ failure–free days, and analyzed these fractional ranks by using analysis of covariance (40). For in-hospital survival data, we used a Cox proportional hazards model (41).

We censored missing data on patients who were lost to follow-up, which was mostly due to out-of-hospital transfer and was unrelated to any risk for death. Overall, 16 patients were censored overall before day 180 of the study, and none was censored before day 28. We used an ordinal logistic regression model for 28-day recovery landmark data (42). Model assumptions were assessed with a test of proportional odds (43) for the ordinal logistic regression model and with a rho statistic (44) for the proportional hazards model. We used a two-sided Wald test (45) to compare age groups. The number of missing values for covariates were 0 for age, race/ethnicity, sex, and treatment assignment; 6 for APACHE III score; 15 for radiographic lung injury score; and 1 for number of organ failures. The multivariable analyses included 881 patients with complete information on all covariates. In all analyses, we considered P values less than 0.05 to be statistically significant.

To perform logistic regression, we used SAS software, version 8.02 (SAS Institute, Inc., Cary, North Carolina); for all other calculations, we used the R system (available at http://cran.r-project.org). We report interquartile ranges.

Role of the Funding Source

The funding agencies had no role in the collection, analysis, and interpretation of the data or approval or disapproval of the finished manuscript.

RESULTS

Baseline Characteristics

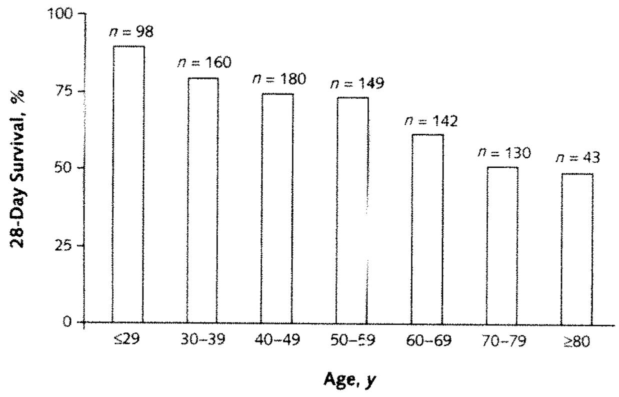
Table 1 shows demographic, physiologic, and radiographic characteristics of patients. The two study

Table 2. **Selected Outcomes at 28 Days in Patients with Acute Lung Injury**

Category	Patients < 70 Years of Age (n = 729)	Patients ≥ 70 Years of Age (n = 173)	*P* Value
Duration of mechanical ventilation, *d**	10 (5 to 26)	19 (7 to >28)	<0.001
Time in intensive care unit, *d**	16 (8 to >28)	21 (11 to >28)	0.004
28-day survival rate, %	74.6	50.3	<0.001

* Values are expressed as the median (interquartile range). The data include survivors and nonsurvivors.

Figure 1. **Histogram of 28-day survival by decade of age.**



Depicted is the decrease in survival seen in patients with acute lung injury by decade of age (Spearman rho = 0.25; $P < 0.001$ for comparison across all groups). The number of patients enrolled in each age group is listed above the bars; the bars represent the percentage of survivors at 28 days for each age group.

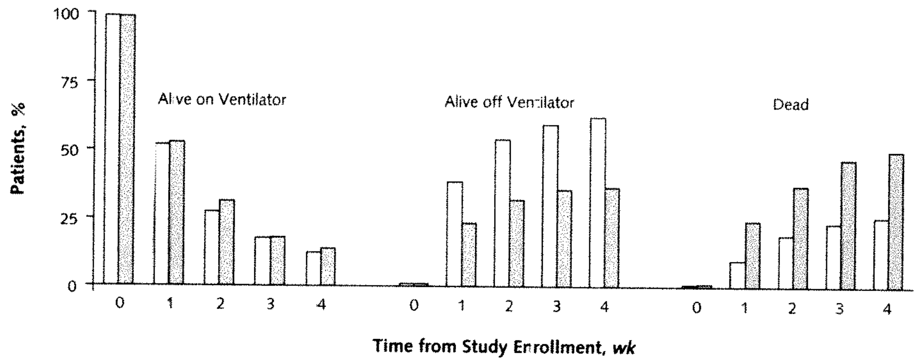
groups included 729 patients younger than 70 years of age (median age, 46 years) and 173 patients 70 years of age or older (median age, 75 years). Despite a 30-year difference in mean age, baseline severity-of-illness scores (the modified APACHE III scores) were nearly identical between the two age groups, as were the baseline number of chest radiography quadrants with infiltrates and the number of nonpulmonary organ system failures. Primary causes of acute lung injury were similarly distributed between younger and older patients, except for aspiration and multiple transfusions (more occurred in the group age ≥ 70 years; $P = 0.003$ and $P = 0.009$, respectively) and trauma (more in the group age < 70 years; $P = 0.009$).

Lengths of Stay and Mortality

The older patients (≥70 years of age) had a higher median duration of mechanical ventilation and length of stay in the intensive care unit and a lower 28-day survival rate ($P < 0.01$ for each comparison) (**Table 2**). Survival at day 28 decreased with increasing decade of age (**Figure 1**) (Spearman rho = 0.25; $P < 0.001$). **Figure 2** shows the status of younger and older patients at weekly intervals. The fraction of younger and older patients alive and receiving mechanical ventilation at each weekly interval was nearly identical, and almost 1 in 5 patients (18%) in both age groups remained on the ventilator for 3 or more weeks. However, at each time point, the older patients were less often alive off the ventilator and more often dead.

The proportion of patients discharged alive and without ventilator support at 180 days was 70.2% (95% CI, 67.0% to 73.6%) in the patients younger than 70 years of age and 40.8% (CI, 34.1% to 48.9%) in the patients 70 years of age or older ($P < 0.001$). For the 861 patients who participated in the ventilator trial of lower versus traditional tidal volume, older and younger

Figure 2. **Histogram of patient outcomes—time on ventilator and death.**



This plot compares the percentage of patients younger than 70 years of age (*white bars*) with the percentage of patients at least 70 years of age (*gray bars*) who were alive on the ventilator, alive off the ventilator, or dead at weekly intervals. At each time point, the percentages of younger and older patients who were alive and receiving mechanical ventilation (*far left*) were nearly identical ($P = 1.0$), but the older patients were less often alive off the ventilator (*center*) and more often dead (*far right*).

Table 3. **Maximum Recovery Landmark Achieved by Day 28 in Survivors and Nonsurvivors***

Stage of Recovery	Survivors	Nonsurvivors	Total
	n (%)		*n*
No recovery beyond baseline	26 (4.1)	162 (59.8)	188
Passed physiologic recovery screen†	40 (6.3)	57 (21.0)	97
Passed 2-hour breathing trial‡	37 (5.9)	30 (11.1)	67
Unassisted breathing for 48 hours§	56 (8.9)	8 (3)	64
Discharged from ICU alive and off mechanical ventilation	515 (74.8)	14 (5.2)	486
Total	631	271	902

* ICU = intensive care unit.

† Physiologic recovery screen of "readiness" to attempt spontaneous breathing included oxygen saturations greater than 0.88 on positive end-expiratory pressure of 8 cm H_2O or less and 0.40 or less fraction of inspired oxygen, systolic blood pressure of 90 mm Hg or higher, and demonstrating spontaneous inspiratory efforts.

‡ Spontaneous breathing trials were conducted by using continuous positive airway pressure of 5 cm H_2O with no pressure support ventilation for up to 2 hours.

§ Unassisted breathing refers to breathing that was extubated, on T-piece, or on continuous positive airway pressure of 5 cm H_2O without pressure support ventilation. If continuous breathing lasted for 48 hours or more, the patient was considered to have passed this stage of recovery.

patients were equally distributed between both treatment groups. Assignment to receive lower tidal volume instead of traditional tidal volume resulted in the same magnitude of absolute risk reduction in mortality at 28 and 180 days for younger and older patients at 28 days (absolute risk reduction for patients < 70 years of age, 9.1 vs. 9.9 percentage points at 28 days and 8.1 vs. 8.6 percentage points at 180 days; $P > 0.2$ for both comparisons).

Progression through Recovery Landmarks

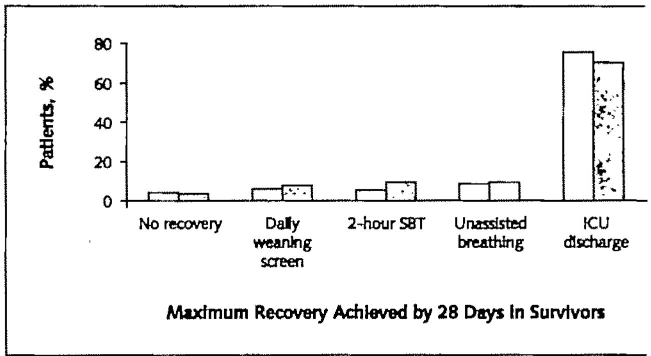
To understand the likelihood and rate of progression of patients through recovery landmarks, we divided the patients into survivors and nonsurvivors and plotted the maximum stage of recovery achieved by day 28 (Table 3). Of the 902 total patients, 631 (70%) survived and 271 (30%) died in the first 28 days. Seventy-five percent of survivors progressed to successful discharge from the intensive care unit alive and without mechanical ventilation by 28 days. In contrast, a similar proportion of nonsurvivors (8 of 10 patients) had either no improvement or only minimal recovery (that is, they never passed a 2-hour spontaneous breathing trial) before death.

Among survivors of acute lung injury, the percentage of patients achieving the recovery landmarks were similar in both age groups ($P > 0.2$) (**Figure 3**). This was also true for the nonsurvivors (data not shown; $P > 0.2$).

Figure 4 depicts the mean times to progress through recovery landmarks by age group. The data for time are shown as intervals between recovery landmarks and are not additive because a cohort is changing from landmark to landmark. Among 28-day survivors, 73 of 87 older patients (83.9%) and 464 of 544 younger patients (85.3%) passed a 2-hour spontaneous breathing trial. The median time from enrollment to passing the spontaneous breathing trial was 4 days (interquartile range, 2 to 9) in older patients and 5 days (interquartile range, 3 to 10) in younger patients ($P > 0.2$). However, after passing the spontaneous breathing trial, older patients required more time to achieve completely unassisted breathing (median time [interquartile range], 1 day [0 to 6 days] for the older group vs. 0 days [0 to 2 days] for the younger group; $P = 0.002$) and to be discharged from the intensive care unit without ventilator support (median [interquartile range], 6 days [2 to 17 days] for the older group vs. 3 days [2 to 8 days] for the younger group; $P = 0.005$). For nonsurvivors, the time to progress through each recovery landmark was similar between old and young patients (data not shown; $P > 0.2$ for each landmark comparison).

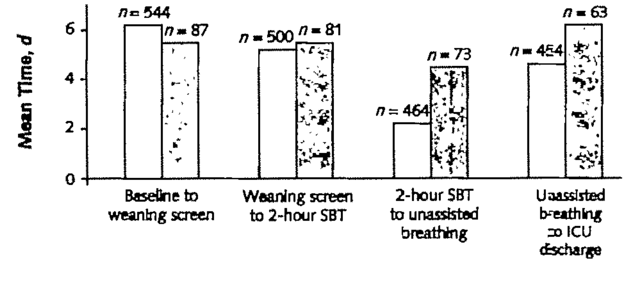
Reintubation rates for patients 70 years of age or older compared with patients younger than 70 years of age were 16.7% (CI, 13.1% to 19.6%) and 7.5% (CI, 5.2% to 10.2%), respectively ($P = 0.027$). The older

Figure 3. **Histogram of maximum recovery landmark achieved by 28 days among survivors.**



The percentage of patients ($n = 631$) who achieved the recovery landmarks (as defined in Methods section) was similar between the group 70 years of age or older (*gray bars*) and the group younger than 70 years of age (*white bars*) ($P > 0.2$). ICU = intensive care unit; SBT = spontaneous breathing trial.

Figure 4. **Histogram of the rate of progress through recovery landmarks achieved by 28 days among survivors.**



The mean time from enrollment to passing a 2-hour spontaneous breathing trial was similar between both age groups ($P > 0.2$) (*white bars* = younger patients; *gray bars* = older patients). However, the older patients took more time to progress from passing the 2-hour spontaneous breathing trial (*SBT*) to achieving 48 hours of unassisted breathing ($P = 0.002$) and from 48-hour unassisted breathing to being discharged from the intensive care unit (*ICU*) without use of a ventilator ($P = 0.005$). Among *nonsurvivors*, the patients 70 years of age or older did not differ from those younger than 70 years of age for any of these time intervals (data not shown; for all time intervals, $P > 0.2$).

group had fewer preexisting comorbid illnesses (according to the chronic health component of the APACHE III scores) than the younger group (13.2% [CI, 10.1% to 16.4%] vs. 21.4% [CI, 18.6% to 24.1%]; $P = 0.02$).

Effect of Age on Outcomes in Multivariable Analysis

Achieving Recovery Landmarks

In a logistic regression analysis without adjustment for survival status, age predicted achievement for all landmark recovery points (Table 4). However, after adjustment for survival status, the only difference in achieving recovery landmarks was that unassisted breathing was achieved less frequently among older survivors than among younger survivors (odds ratio, 0.48 [CI, 0.27 to 0.85]; $P = 0.01$). In keeping with these findings, multivariable Cox regression analysis (stratified by treatment center and adjusted for other covariates but not survival status) showed that age predicted the duration of mechanical ventilation (hazard ratio, 0.60 [CI, 0.46 to 0.77]) and duration of stay in the intensive care unit (hazard ratio, 0.71 [CI, 0.54 to 0.93]). However, again, after adjustment for survival status the two age groups did not differ except for amount of time receiving ventilator support: Older patients tended to have a longer duration of mechanical ventilation (hazard ratio, 0.76 [CI, 0.58 to 1.01]; $P = 0.056$). The proportional hazard assumptions were satisfied for the age groups.

Survival and Organ Failure

Multivariable Cox regression analysis (stratified by treatment center and adjusted for other covariates) showed that age of 70 years or older was a strong predictor of in-hospital death, with a hazard ratio for death of 2.5 (CI, 2.0 to 3.2; $P < 0.001$). The model satisfied proportional hazards assumptions. Analysis of covariance with organ failure–free days revealed that older persons had more coagulation failure–free days than did younger patients (that is, persons ≥ 70 years of age had more days with a platelet count $> 80 \times 10^9$ cells/L than patients < 70 years of age) ($P = 0.03$). We detected no difference between age groups in the number

Table 4. **Logistic Regression: Effect of Age on Achieving Recovery Landmarks***

Recovery Landmark, Type of Analysis	Odds Ratio for Persons ≥ 70 Years of Age (95% CI)	P Value
Passed physiologic recovery screen†		
All patients	0.469 (0.317–0.695)	<0.001
All patients, adjusted for survival	0.894 (0.551–1.451)	>0.2
Nonsurvivors only	0.708 (0.379–1.320)	>0.2
Survivors only	1.137 (0.448–2.888)	>0.2
Passed spontaneous breathing trial‡		
All patients	0.410 (0.281–0.599)	<0.001
All patients, adjusted for survival	0.754 (0.463–1.228)	>0.2
Nonsurvivors only	0.639 (0.288–1.417)	>0.2
Survivors only	0.860 (0.435–1.699)	>0.2
Unassisted breathing for 48 hours§		
All patients	0.349 (0.239–0.509)	<0.001
All patients, adjusted for survival	0.583 (0.350–0.973)	0.039
Nonsurvivors only	0.900 (0.295–2.743)	>0.2
Survivors only	0.476 (0.267–0.849)	0.012
ICU discharge		
All patients	0.439 (0.302–0.639)	<0.001
All patients, adjusted for survival	0.846 (0.511–1.398)	0.513
Nonsurvivors only	1.128 (0.266–4.786)	>0.2
Survivors only	0.805 (0.465–1.395)	>0.2

* ICU = intensive care unit.

† Physiologic recovery screen of "readiness" to attempt spontaneous breathing included oxygen saturations greater than 0.88 on positive end-expiratory pressure of 8 cm H_2O or less and 0.40 or less fraction of inspired oxygen, systolic blood pressure of 90 mm Hg or higher, and demonstrating spontaneous inspiratory efforts.

‡ Spontaneous breathing trials were conducted by using continuous positive airway pressure of 5 cm H_2O with no pressure support ventilation for up to 2 hours.

§ Unassisted breathing refers to breathing that was extubated, on T-piece, or on continuous positive airway pressure of 5 cm H_2O without pressure support ventilation. If continuous breathing lasted for 48 hours or more, the patient was considered to have passed this stage of recovery.

of central nervous, circulatory, hepatic, or renal failure–free days ($P > 0.2$ for each comparison).

DISCUSSION

Our analysis of this large cohort of patients with acute lung injury has important implications for advancing the care of older patients with respiratory failure. Patients 70 years of age or older had 28-day and 180-day mortality rates that were nearly twice those of patients younger than 70 years of age. Even after adjustment for covariates, we found that age was a strong predictor of mortality. In fact, older persons had a hazard ratio of 2.5 for in-hospital death, and varying the age cut-off by using 65 or 80 years of age did not alter the significance of these results. Our finding with the greatest implications for patient management was that surviving older persons achieved initial recovery landmarks at the same rates as their younger counterparts (the older age group passed conventional weaning criteria and could sustain spontaneous breathing without mechanical support) yet were delayed in their further progression through convalescence and were much more likely to be reconnected to the ventilator.

Three recent reports (9, 46, 47) of patients with respiratory failure requiring mechanical ventilation are particularly relevant to our findings. These studies demonstrated that younger and older patients spent similar amounts of time receiving mechanical ventilation but reported contradictory results for the ultimate outcome—mortality. One study (47) found that patients with acute lung injury older and younger than 55 years of age had similar durations of mechanical ventilation, but the researchers observed a trend toward a *lower* mortality rate in patients older than 70 years of age. A subsequent report from a medical intensive care unit showed that mechanically ventilated older persons (with respiratory failure from various causes, *not* confined to acute lung injury) had durations of ventilator support and rates of survival that were similar to those of their younger counterparts (9). This cohort was from a single center, in which local triage decisions may have introduced selection bias by enrolling older persons with fewer comorbid illnesses, who would be more likely to survive their respiratory failure (9). Finally, an abstract from an international study of respiratory failure from diverse causes showed that the 1038 participants at least 75 years of age had similar durations of mechanical ventilation and in-hospital stay compared with the 4118 participants younger than 75 years of age ($P > 0.2$ for both comparisons) (42). However, in that large report, the older patients did have higher mortality rates in the intensive care unit (38% vs. 30%; $P < 0.001$) and in the hospital overall (52% vs. 37%; $P < 0.001$) compared with the younger patients. Our study builds on these data by focusing on acute lung injury, which is generally considered the most fulminant type of respiratory failure and thus potentially more difficult to tolerate in older persons.

The duration of mechanical ventilation has been shown to independently predict mortality, even after adjustment for covariates such as severity of illness (48). It is imperative that clinicians liberate patients from mechanical ventilation at the optimal time, thereby reducing complications, pain and suffering, and expenses. The landmark most frequently used in ventilator weaning protocols to signify patient readiness for extubation and independence from a ventilator has been the ability to breathe spontaneously (29, 31, 49–52). Consistent with our earlier report (9), the current study found that lung recovery to the point of passing spontaneous breathing trials occurred at the same rate in younger and older patients. However, although all patients were managed with the same detailed protocol, older patients required 1 day more than younger patients after passing spontaneous breathing trials to achieve at least 48 hours of unassisted breathing and required 3 more days before successful discharge from the intensive care unit.

These age-related differences in mortality and outcomes during late stages of mechanical ventilation may be due to the greater number of comorbid illnesses and higher frequency of nonpulmonary organ system failure in older persons. Some researchers have suggested that the long-term outcome of respiratory failure may depend less on the severity of the respiratory failure than on other factors (21, 53); for example, occult cardiovascular disease could place patients at risk for developing ischemia and subsequent cardiac complications during weaning (54, 55). Surprisingly, our data showed that older patients may have entered the study with a lower preexisting burden of illness (that is, the older population had fewer points for the chronic health component of the APACHE III scores), but we had not designed our study to detect such occult diseases or to adequately calculate comorbid illnesses. Regarding nonpulmonary organ system failures, we found that older patients experienced more failure-free days for the coagulation system (older patients had thrombocytopenia less frequently), but the durations of dysfunction for other organ systems appeared similar between the two age groups. How the coagulation system might have influenced clinical outcomes remains poorly understood, and this may be elucidated through ongoing research efforts into interactions of inflammation, coagulation, and organ failure (56–60).

The most consistent message from our analyses was that older patients, regardless of similar rates of initial physiologic recovery compared with younger patients, had delayed liberation from the ventilator even after adjustment for survival status. Of note, the reintubation rate for the older patients was more than twice that for the younger patients; in general, reintubation has been found to increase independently the risk for adverse outcomes such as nosocomial pneumonia and death (50, 51, 61, 62). Although the prognostic importance of the cause and timing of reintubation are well recognized (63), these data were not recorded in this investigation. In addition to the potential effect of other occult nonpulmonary organ dysfunctions, central nervous system disease may have contributed to the age disparity in outcomes. It is worth acknowledging that older patients are at higher risk for having baseline central nervous system diseases, such as dementia or cerebrovascular accidents, or for developing profound delirium while in the intensive care unit (64–70). Such neurologic disturbances were poorly monitored in this cohort; however, such disturbances may directly affect the latter stages of mechanical ventilation (for example, after passing a spontaneous breathing trial) by interfering with the ability to protect the upper airway, with physical therapy, and with attempts to mobilize the patient—thus limiting successful liberation from the ventilator (71–73). This could prolong intubation, lead to reintubation, and further increase the risk for subsequent nosocomial pneumonia or even death (50, 61, 74). Recent protocol advancements regarding sedation and analgesia (75, 76), monitoring of delirium in the intensive care unit (68, 69), and screening for baseline or long-term cognitive impairments (77–80) might enhance our ability to detect and prevent such abnormalities and may help improve quality of life (81) for older survivors of acute lung injury.

Future investigations could improve upon several of the limitations in our study. For example, we did not evaluate whether a lower threshold for do-not-resuscitate orders and withdrawal of life support in older persons may have contributed to the higher mortality rates in this age group (6, 7, 47). Because of the specific ventilator protocol used in this study, we could not investigate the utility of modifying weaning criteria according to age. However, age-related differences in perceptions of dyspnea (82), vital sign abnormalities (53), or breathing patterns (83) could affect clinicians' decisions and should be incorporated into the designs of future weaning investigations or guidelines (84). We tracked organ failures but did not analyze the cumulative effect of preexisting comorbid illness, which can be difficult to calculate (85). Important areas of organ-system dysfunction probably were not measured adequately—for example, systematically capturing the presence of coronary or other occult organ disease, impaired nutritional status (86), or iatrogenic complications, such as specific types and quantities of sedatives and analgesics—and these factors certainly could contribute to more central nervous system dysfunction in older persons. We also had no data on the criteria used to determine patient readiness for discharge from the intensive care unit. These uncontrolled aspects of care and other unobserved confounders may have affected our results.

In conclusion, we found that although older persons with acute lung injury had survival rates at 28 and 180 days of 50% and 40%, respectively, at both time points they were twice as likely to die compared with their younger counterparts. In our opinion, these data do not suggest that physicians (or society) should be directing resources or life support away from elderly patients with acute lung injury. Rather, future efforts should be directed to improve the outcomes of older patients with acute lung injury. In this study, older persons were able to recover sufficiently from a respiratory perspective to achieve spontaneous breathing at the same rate as younger patients. Despite this recovery, however, our data showed that older persons had greater difficulty progressing through the late stages of convalescence and achieving unassisted breathing for more than 48 hours. Therefore, it may be important to alter management decisions for older persons throughout their stay in the intensive care unit to better prepare these patients to remain unassisted and liberated from the ventilator once they have passed readiness testing. In addition, attention to the details of care at the time of and immediately following liberation from the ventilator appears particularly important in older patients.

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Anomalies of the Inferior Vena Cava in Patients with Iliac Venous Thrombosis

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Background: Cases of deep venous thrombosis in the lower extremities triggered by abnormalities of the vena cava have been reported.

Objective: To describe anomalies of the inferior vena cava in patients with deep venous thrombosis.

Design: Prospective, consecutive case series.

Setting: University Hospital, Graz, Austria.

Patients: 97 patients with deep venous thrombosis.

Intervention: Sonography, venography, or both to diagnose deep venous thrombosis; magnetic resonance angiography to image the inferior vena cava.

Measurements: Anomalies of the inferior vena cava imaged by magnetic resonance angiography.

Results: 31 of 97 patients showed thrombotic occlusion of iliac veins (common and external iliac vein [*n* = 29] or external iliac vein [*n* = 2]). Five of 31 patients (3 men, 2 women) had an anomaly of the inferior vena cava. Anomalies were missing inferior vena cava, hypoplastic hepatic segment, and missing renal or postrenal segments. Patients with anomalies were significantly younger than the 92 patients without (mean age ± SD, 25 ± 6 years vs. 53 ± 19 years; $P = 0.002$). In 2 patients with anomalies, the thrombotic occlusion was recurrent.

Conclusions: An anomaly of the inferior vena cava should be suspected if thrombosis involving the iliac veins is seen in patients 30 years of age or younger. Patients with both an anomaly and thrombosis may be at higher risk for thrombotic recurrence.

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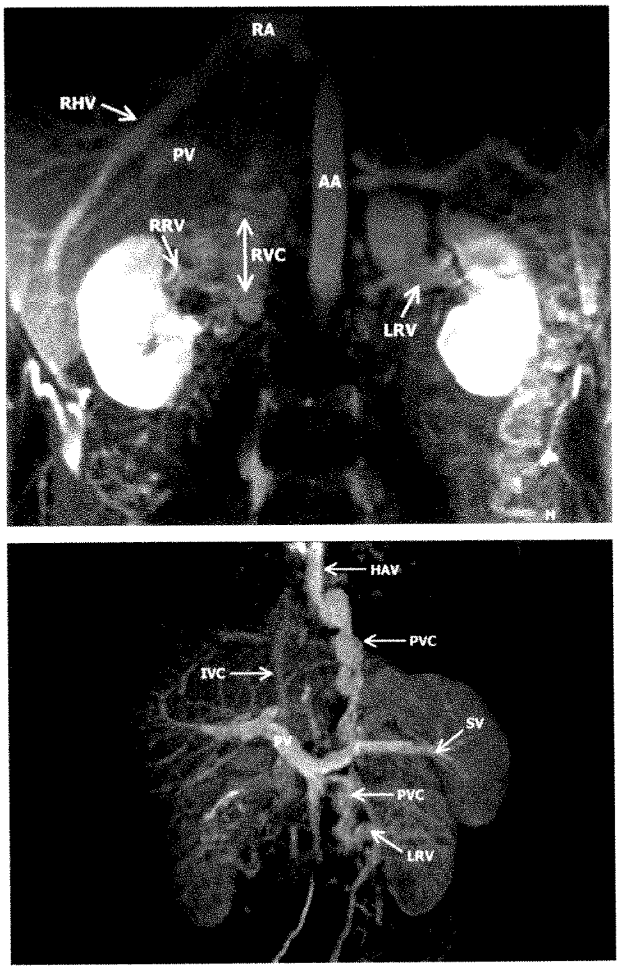
During embryogenesis, the inferior vena cava is formed by a process involving the development, regression, and anastomosis of three sets of paired veins: the posterior cardinal, subcardinal, and supracardinal veins (1). The normal inferior vena cava is converted to a unilateral right-sided system consisting, from cauda to cranium, of the postrenal, renal, prerenal, and hepatic segments. If the originally paired structures do not unite, however, anomalies of the inferior vena cava may result. Such anomalies have an estimated prevalence of 0.07% to 8.7% in the general population (2). Anomalies become apparent in infants when combined with heart failure or visceral malformations (3). In adults, anomalies are commonly seen incidentally in abdominal surgery or in radiologic work-up (2, 4, 5). However, some case reports have identified patients with anomalies of the inferior vena cava that became symptomatic because of deep venous thrombosis of the iliac veins (5–13). In this study, we identified anomalies of the inferior vena cava in consecutive patients with deep venous thrombosis in the lower extremities.

METHODS

We studied 97 consecutive patients (51 men, 46 women; mean age ± SD, 51 ± 19 years) who presented with confirmed deep venous thrombosis in the lower extremities from October 1997 to June 1999. Forty-nine patients had left deep venous thrombosis, 34 had right deep venous thrombosis, and 14 had bilateral deep venous thrombosis.

Deep venous thrombosis in the lower extremities was confirmed by color-coded duplex sonography (using 5- and 7-MHz linear transducers [Acuson 128 XP/10, Mountain View, California]), ascending venography according to the technique of Hach (14), or both. Ascending venography was performed in all patients when duplex sonography indicated a thrombotic occlusion of the iliac veins (common iliac and external iliac veins). Thrombotic occlusion of the iliac veins was suspected when the iliac veins could not be completely visualized and poor blood flow with loss of cyclic respiratory variations was seen at the level of the common femoral vein (15). If ascending venography showed no enhancement of contrast medium or only poor filling of the inferior vena cava, abdominal, gadolinium-enhanced, breath-hold, three-dimensional, three-phase magnetic resonance angiography was performed (1,5 Tesla Gyroscan ACS-NT, Philips, Eindhoven, the Netherlands) (16). Abdominal and pelvic computed tomography was performed to exclude pelvic masses obstructing the venous

Figure. **Single slices of abdominal, gadolinium-enhanced magnetic resonance angiograms demonstrating anomalies of the inferior vena cava (*IVC*) in patient 1 (*top*) and patient 2 (*bottom*).**



In patient 1, the IVC is missing. Tortuous renal venous collaterals (*RVCs*) collect the venous blood return from both patent renal veins and drain into the azygous vein (not visible), which is enlarged to compensate for the anomaly. The right hepatic vein (*RHV*) enters directly into the right atrium (*RA*). In patient 2, the hepatic segment of the IVC is tiny and hypoplastic. The hemiazygous vein (*HAV*), which is enlarged to compensate for the anomaly, collects the venous blood return from markedly dilated paravertebral venous collaterals (*PVCs*). The renal segment of the IVC is missing, and the left renal vein (*LRV*) drains to paravertebral venous collaterals. AA = abdominal aorta; PV = portal vein; RRV = right renal vein; SV = splenic vein.

blood flow. Screening for thrombophilia (including tests for activated protein C resistance time, factor V Leiden, levels of protein C and protein S, and presence of antithrombin III and phospholipid antibodies) was routinely performed in all patients.

We used the unpaired Student *t*-test to compare the mean age of patients who had inferior vena cava anomalies with that of patients who did not. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Thirty-one of 97 patients had thrombotic occlusion of iliac veins (left [n = 22], right [n = 5], or bilateral [n = 4]). Of these 31 patients, 29 had occlusion of the common and external iliac vein and 2 had occlusion of the external iliac vein. In 5 patients (3 men, 2 women), an anomalous inferior vena cava was diagnosed by magnetic resonance angiography. Anomalies were an absent inferior vena cava, a hypoplastic hepatic segment, and absent renal or postrenal segments. The missing segments of the inferior vena cava were replaced by an enlarged venous collateral system (**Figure**). Patients with an anomaly of the inferior vena cava were significantly younger than those without such anomalies (mean age ± SD, 25 ± 6 years vs. 53 ± 19 years; $P = 0.002$). Screening tests for thrombophilia in 97 patients revealed a resistance to activated protein C associated with heterozygous mutation for factor V Leiden in 8 patients, protein S deficiency in 1 patient, and antiphospholipid syndrome in 2 patients.

Patient 1 presented with a painfully swollen left leg. Swelling had persisted for 2 weeks after strenuous physical exertion (fitness training and bodybuilding). Two years before, patient 1 had received surgical treatment for thrombotic occlusion of the right common and external iliac vein. Although the surgery was primarily successful, it was followed by ipsilateral reocclusion and contralateral occlusion of the common and external iliac veins. It was noted intraoperatively that cannulation of the inferior vena cava was impossible. The patient received oral anticoagulation for 1 year.

Patient 2 presented with lumbar pain 1 day after a strenuous bicycle tour. Both thighs swelled 4 days later. Patient 3 was admitted with pain in the left inguinal region 1 day after a long-distance car ride. Additional thrombogenic risk factors were the use of oral contraceptives for the previous 3 months and a protein S level that had decreased to 0.46 (normal range, 0.7 to 1.4). Patient 4 was admitted 4 days after a long-distance bus ride and had had pain, swelling, and redness of the left leg for the 2 previous days. Patient 5 was admitted with persistent swelling and pain in the left leg after several days of strenuous labor as a lumberjack. Six years before admission, he had undergone unsuccessful surgery for a right-sided thrombotic occlusion of the common and external iliac veins. The patient received oral anticoagulation for 2 years.

Demographic characteristics, location of previous and acute thrombosis, treatment, thrombophilic state, type of inferior vena cava anomaly, and other existing vascular anomalies are summarized in the **Table**. Continuous therapy for all 5 patients included oral anticoagulation and elastic supports. At follow-up (7 to 21 months), thrombotic recurrence was suspected in 1 patient but was excluded by venography. Three patients were free of symptoms, and 1 patient declined further examination.

No concomitant visceral defects or neuropathic findings were detected in any of the patients. Magnetic resonance angiography of the patients' family members showed that the fraternal twin sister of patient 1 had a normally developed inferior vena cava and that the brother of patient 5 had a duplicate right renal artery but a normally developed inferior vena cava.

DISCUSSION

In our study, 5 of 31 patients with thrombotic involvement of iliac veins had anomalies of the inferior vena cava. Proximal deep venous thrombosis was diagnosed by duplex sonography, venography, or both. The sensitivity of duplex sonography in detecting proximal deep venous thrombosis ranges from 92% to 95%, and specificity ranges from 97% to 100% (17). Venography is the reference method for diagnosing deep venous thrombosis (17). Anomalies of the inferior vena cava were confirmed by magnetic resonance angiography, a method of depicting venous abnormalities that is highly sensitive and specific and does not use ionizing radiation (16).

Anomalies of the inferior vena cava are caused by aberrant development in the sixth to eighth weeks of gestation. During this period, complex embryologic development of the inferior vena cava with anastomoses, disappearance, and replacement of vessels may result in various types of malformations (1, 2). If the deep venous collateral system is sufficiently developed and drains the venous blood from the lower extremities to the heart, symptoms are likely to be prevented in a patient with anomalies of the inferior vena cava (7, 10). In patients at risk for thrombogenic events, however, an inadequate blood return through collaterals may increase the venous blood pressure in the veins of the legs, favoring venous stasis and subsequent deep venous thrombosis (6, 9–11, 13).

We investigated consecutive patients with deep venous thrombosis in the lower extremities and found concomitant iliac vein thrombosis and anomalies of the inferior vena cava in 5 patients. Patients with anomalies were significantly younger than the 92 patients without ($P = 0.002$). In the literature, the mean age (±SD) of the patients with such anomalies is 33 ± 12 years; some patients presented with recurrent thrombotic events and post-thrombotic complications (8–11).

Table. **Characteristics of Patients with Anomalies of the Inferior Vena Cava***

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Male	Male	Female	Female	Male
Age, y	25	24	22	20	35
Location of previous thrombosis	LCIV, LEIV, RCIV, REIV	–	–	–	RCIV, REIV
Location of acute thrombosis	LCFV, LSFV	LCIV, LEIV, LCFV, LSFV, RCIV, REIV, RCFV, RSFV	LCIV, LEIV	LCIV, LEIV, LCFV, LSFV	LCIV, LEIV, LCFV, LSFV
Thrombophilia	–	–	Protein S deficiency	–	–
Type of treatment	Anticoagulant	Thrombolytic (failed)	Thrombolytic (failed)	Anticoagulant	Anticoagulant
Anomaly of the inferior vena cava on MRA	No inferior vena cava	Hypoplastic hepatic segment, absent renal segment	Hypoplastic hepatic segment, absent renal and postrenal segments	Absent postrenal segment	Hypoplastic hepatic segment
Other vascular anomalies	–	Triplicate right renal artery, duplicate left renal artery	–	–	Duplicate right renal artery

* LCFV = left common femoral vein; LCIV = left common iliac vein; LEIV = left external iliac vein; LSFV = left superficial femoral vein; MRA = magnetic resonance angiography; RCFV = right common femoral vein; RCIV = right common iliac vein; REIV = right external iliac vein; RSFV = right superficial femoral vein.

In our study, strenuous muscular exercise, physical effort, long car and bus rides, and a strenuous bicycle tour may have triggered the acute thrombotic events. Patients who are known to have anomalies of the inferior vena cava should be advised to avoid additional thrombogenic risk factors, such as unusual physical efforts, prolonged immobilization, and oral contraceptive use (5). Patients with persistent risk factors and symptomatic deep venous thrombosis are at high risk for thrombotic recurrence (18). Two patients in our study presented with recurrent deep venous thrombosis after discontinuation of oral anticoagulation. Economic evaluations have shown that prophylactic measures are cost-effective in preventing recurring thromboembolism and its long-term complications, compared with no prophylaxis or surveillance and selective treatment of venous thromboembolism (19).

Our study has several limitations. First, we may have underestimated the number of anomalies of the inferior vena cava because magnetic resonance angiography was performed only when venography indicated a possible abnormality. Because only a small number of patients in our selected study sample had anomalies of the inferior vena cava, generalization of our results may not be justified. However, patients with an acquired thrombotic occlusion of the inferior vena cava may have a similar risk for deep venous thrombosis in the lower extremities. In our study, the absence of inferior vena cava segments was not the consequence of an acquired thrombotic occlusion. The latter is a serious clinical event, and symptoms vary with the level of occlusion (20). The absence of clinical symptoms before the first thrombotic manifestation and the absence of inferior vena cava segments in all slices of magnetic resonance angiography suggest that the anomalies in our study were congenital rather than acquired.

Our results indicate that an anomalous inferior vena cava should be suspected in patients 30 years of age or younger who have thrombosis involving the iliac veins. Patients with an anomaly of the inferior vena cava and deep venous thrombosis may be at higher risk for thrombotic recurrence.

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The Risk–Benefit Profile of Commonly Used Herbal Therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava

Edzard Ernst, MD, PhD, FRCP(Edin)

Because use of herbal remedies is increasing, a risk–benefit profile of commonly used herbs is needed. This article provides a clinically oriented overview of the efficacy and safety of ginkgo, St. John's wort, ginseng, echinacea, saw palmetto, and kava. Wherever possible, assessments are based on systematic reviews of randomized clinical trials. Encouraging data support the efficacy of some of these popular herbal medicinal products, and the potential for doing good seems greater than that for doing harm. The published evidence suggests that ginkgo is of questionable use for memory loss and tinnitus but has some effect on dementia and intermittent claudication. St. John's wort is efficacious for mild to moderate depression, but serious concerns exist about its interactions with several conventional drugs. Well-conducted clinical trials do not support the efficacy of ginseng to treat any condition. Echinacea may be helpful in the treatment or prevention of upper respiratory tract infections, but trial data are not fully convincing. Saw palmetto has been shown in short-term trials to be efficacious in reducing the symptoms of benign prostatic hyperplasia. Kava is an efficacious short-term treatment for anxiety. None of these herbal medicines is free of adverse effects. Because the evidence is incomplete, risk–benefit assessments are not completely reliable, and much knowledge is still lacking.

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Physicians' need for reliable information on herbal medicinal products is considerable. In the United States, the popularity of complementary and alternative medicine is growing at a remarkable and perhaps disquieting speed (1). Herbal medicine has grown faster than any other "alternative" treatment method in the United States (1, 2). The seven top-selling herbal medicinal products in the United States are *Ginkgo biloba* (total 1998 retail sales of $151 million), St. John's wort ($140 million), ginseng ($96 million), garlic ($84 million), echinacea ($70 million), saw palmetto ($32 million), and kava ($17 million) (3). (Garlic is not discussed in this article; the reader is referred to two recent meta-analyses [4, 5].)

Physicians regularly see patients who self-prescribe herbal medicinal products but do not volunteer this information (1). Many herbal medicines have adverse effects, and most can interact with purified prescription drugs (6). A complete medical history should therefore include specific questions about the use of herbal medicinal products (7), and physicians must acquire sufficient knowledge in this area to advise their patients responsibly.

This article provides risk–benefit profiles for the most commonly used herbal medicines. These profiles are based on systematic reviews where possible.

METHODS

Electronic literature searches were done to locate all systematic reviews of gingko, St. John's wort, ginseng, echinacea, saw palmetto, and kava. The MEDLINE (via PubMed), EMBASE, CISCOM, and AMED databases and the Cochrane Library were searched from their inception to October 2000. In addition, nine experts in the field were asked for further details on systematic reviews, and the author's personal files were searched for further articles.

All systematic reviews of randomized clinical trials in humans were included. They were read in full, and key data were extracted according to criteria that appear as column headers in **Table 1**. The quality of the reviews was estimated according to the guidelines of the Quality of Reporting of Meta-analyses statement (23). In essence, the following questions were asked: Are the objectives of the review clearly stated? Are the data sources stated? Are the search methods explained? Are inclusion and exclusion criteria stated? Was the validity of primary data assessed? Is the data abstraction process explained? Were the study characteristics assessed? Are the results adequately discussed? If the answer to seven or more of these nine questions was "yes," the review was rated as "good"; if four to six responses were positive, it was rated as "adequate"; and if three or fewer were positive, it was rated as "poor." Of note, the methodologic quality of a systematic review and that of the primary studies are largely independent: For example, weak clinical trials can be analyzed in a high-quality review.

GINKGO (*GINKGO BILOBA*)

Ginkgo fruits and seeds have been used in traditional Chinese medicine for millennia (mostly to treat

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asthma and chilblains). The flavonoids and terpene lactones from the ginkgo leaf, which today is used for medicinal purposes, are associated with diverse pharmacologic actions (Table 2). In vitro and in vivo studies suggest that ginkgo has antiedemic, antihypoxic, free radical–scavenging, antioxidant, metabolic, antiplatelet, hemorheologic, and microcirculatory actions (8, 24). Ginkgo has been used experimentally for myocardial reperfusion injury, depression, brain trauma, free radical damage to the retina, cochlea deafness, vertigo, male impotence, and asthma (9). In clinical practice, it is used mostly for memory impairment, dementia, tinnitus, and intermittent claudication. In some European countries, ginkgo is registered for these indications; in the United States, it is marketed as a dietary supplement.

Memory Impairment

A rigorous systematic review of high methodologic quality included 40 mostly weak controlled trials of ginkgo for "cerebral insufficiency": memory impairment but not dementia (10). With their own scoring system, the authors judged that only 8 of the primary studies had good methodologic quality. All but 1 of these 8 studies showed positive effects of ginkgo on cognitive function compared with placebo. For global effectiveness ratings and single symptoms (such as forgetfulness), clear evidence favored ginkgo over placebo. However, the authors warn of publication bias because "there were no negative results reported in many trials of low quality" (10). Another, less rigorous meta-analysis studied one standardized extract (11). The author did not formally assess the quality of the primary studies. Of the 11 randomized clinical trials included, 5 had not been included in the previous meta-analysis (10). Again, the conclusions were positive (Table 1).

Thus, encouraging data exist, but the evidence for ginkgo as a memory enhancer is not fully convincing. Contrary to claims often made, no compelling evidence shows that ginkgo enhances normal cognitive function.

Dementia

A systematic review of adequate quality (25) included nine randomized, double-blind, placebo-controlled clinical trials of ginkgo to treat dementia. Methodologic quality of the primary studies was assessed by using the Jadad score, and three studies had the highest possible rating (5 out of 5 points). Eight studies, including the three highest-quality studies, suggested that ginkgo is significantly more effective than placebo in delaying clinical cognitive deterioration in dementia.

Using stricter entry criteria, Oken and colleagues (12) conducted a meta-analysis of high methodologic quality of four randomized, double-blind, placebo-controlled clinical trials of ginkgo to treat Alzheimer disease. All of these studies were included in our analysis (25). The methodologic quality of the primary studies was not formally assessed. Again, the overall result was positive. The pooled effect size in terms of cognitive function was moderate and translated into a 3% difference in the Alzheimer's Disease Assessment Scale–Cognitive subtest (Table 1). Thus, the average effect size associated with ginkgo is likely to be clinically relevant.

Tinnitus

Ginkgo increases fluidity of blood and thus might optimize blood flow at the microcirculatory level (13). These effects prompted testing the clinical efficacy of ginkgo in treating tinnitus. A systematic review of adequate quality (26) summarized all five randomized clinical trials of ginkgo for this indication (Table 1). Methodologic quality of the primary studies was assessed by using the Jadad score, and only one study was deemed to be of sufficient rigor. The results showed a moderate but statistically significant effect of ginkgo extract taken for 12 weeks on the perceived loudness of the tinnitus sound. Because few rigorous trials have been published, the therapeutic value of ginkgo for tinnitus is uncertain.

Intermittent Claudication

Because gingko may optimize microcirculatory blood flow, it has been used to treat intermittent claudication. A meta-analysis of good quality (27) pooled results of eight randomized, double-blind, placebo-controlled clinical trials and calculated the weighted mean difference in pain-free walking distance between the experimental and control groups (Table 1). The methodologic quality of the primary data was assessed by using the Jadad score, and most studies received 5 or 4 points out of the maximum of 5. The results indicate that gingko recipients walked 34 m (95% CI, 26 to 43 m) farther without pain compared with controls. Thus, the effect is moderate yet probably clinically relevant.

Comparative studies of ginkgo and pentoxifylline

Table 1. **Systematic Reviews of Top-Selling Herbal Medicinal Products***

Common Name (Manufacturer)†	Indication	Type of Study (Quality Estimate)	Trials (Patients), *n (n)*	Average Methodologic Quality‡
Ginkgo (Schwabe, Lichtwer)	Memory impairment	Qualitative systematic review (good)	40 (not mentioned)	Only 8 trials were good
		Meta-analysis (adequate)	11 (11 130)	Good, but not formally evaluated
	Dementia	Qualitative systematic review (good)	9 (1497)	Good
		Meta-analysis (adequate)	4 (212)	Good, but not formally evaluated
	Tinnitus	Qualitative systematic review (adequate)	5 (621)	Poor
	Intermittent claudication	Meta-analysis (good)	8 (413)	Very good
St. John's wort (Lichtwer)	Mild to moderate depression	Meta-analysis (good)	23 (1757)	Good
	Depression	Qualitative systematic review (adequate)	6 (881)	Very good
		Qualitative systematic review (good)	8 (985)	Very good, but not formally evaluated
		Qualitative systematic review and meta-analysis (good)	6 (651)	Very good, but not formally evaluated
	Multiple depressive disorders	Meta-analysis (good)	14 (1417)	Very good, but not formally evaluated
Ginseng (Asian) (Pharmaton)	Various	Qualitative systematic review (adequate)	16 (NA)	Mostly poor
Echinacea (Madaus)	Prevention and treatment of upper respiratory tract infection	Qualitative systematic review (good)	16 (3396)	Moderate to good
Saw palmetto (Schwabe)	Benign prostatic hyperplasia	Meta-analysis (good)	18 (2939)	Good
Kava (Schwabe)	Anxiety	Meta-analysis (adequate)	7 (377)	Good

* NA = not applicable.

† The manufacturers listed are those that make herbal medicinal products frequently tested in clinical trials. Their locations are as follows: Schwabe: Karlsruhe, Germany; Lichtwer: Berlin, Germany; Pharmaton: Lugano, Switzerland; and Madaus: Cologne, Germany.

‡ Quality of primary studies, as estimated by the authors of the review (different methods were used).

(the gold standard treatment in Europe for intermittent claudication) suggest that both treatments are similarly effective in increasing the walking distance of patients with claudication (28, 29). However, compared with regular walking exercises, ginkgo is clearly less effective (30).

Safety

Adverse effects of ginkgo are usually mild, transient, and reversible (**Table 3**). Potentially serious adverse effects are bleeding (for example, subdural hematoma) (8, 24) and seizures, which were seen in children after excessive ingestion of seeds (31). Because gingko has antiplatelet activity (6), it may interact with anticoagulants (31, 32); several cases have been reported (14).

Dosage

Adequate dose-finding studies for gingko are not available. Clinical experience and data from randomized clinical trials suggest the therapeutic window is wide. Clinical trials used dosages of 120 to 320 mg/d. The most common dosage is 40 mg of standardized extract of ginkgo leaf thrice daily (24). Quality extracts are characterized by 22% to 27% flavone glycosides and 5% to 7% terpin lactones (2.8% to 3.4% ginkgolides and 2.6% to 3.6% bilobalides) (15). Clinical effects usually emerge after about 4 weeks of treatment. Use of low-quality, nonstandardized extracts should be discouraged.

ST. JOHN'S WORT (*HYPERICUM PERFORATUM*)

St. John's wort, applied topically or systemically, has been used to treat bronchitis, burns, cancer, enuresis, gastritis, hemorrhoids, hypothyroidism, insect bites, insomnia, kidney disease, scabies, and wound healing (31). Today, it is used almost exclusively as an herbal antidepressant. Its mechanism of action is now thought

Table 1—**Continued**

Main Result or Conclusion	Comment	Reference
Ginkgo is superior to placebo, but with caveats	Possible publication bias	8
Ginkgo is superior to placebo	The largest study was not randomized	9
Ginkgo is convincingly superior to placebo	Large variation in dosages used	10
Mean effect size, 0.41 (95% CI, 0.22–0.61)	Effect size equals about 1 SD	11
4 trials were positive (including the most rigorous study)	No firm conclusions because of lack of rigorous trials	12
Average increase in pain-free walking distance, 36.3 m (95% CI, 0.9–1.3 m) compared with reference medications	Effect size is moderate but compares well with those of other oral medications for this condition	13
Odds ratio, 2.5 (95% CI, 1.7–3.6) vs. placebo and 1.1 (95% CI, 0.9–1.2) vs. reference medications	Reference medications were underdosed in several of the comparative trials	14
All placebo-controlled trials favored St. John's wort	One trial also suggested efficacy in severe depression	15
All placebo-controlled trials favored St. John's wort	Review also included 1 positive trial in severe depression	16
Relative risk, 1.48 (95% CI, 1.03–1.92) in favor of St. John's wort	Authors criticized the short duration of studies	17
Relative benefit of 1.9 over placebo and 1.2 over tricyclic antidepressants	6 studies on major depression were included; possible publication bias	18
No indication is supported by compelling evidence	Epidemiologic data suggest that regular intake may minimize cancer risk	19
Some preparations have a better effect than placebo	Considerable lack of uniformity among studies; possible publication bias	20
Superior to placebo and equivalent to finasteride	No long-term data available	21
Weighted mean difference in Hamilton Anxiety Scale score of 9.7 (95% CI, 3.5–15.8)	Only symptomatic therapy, and only short-term	22

to lie in selective inhibition of serotonin, dopamine, and norepinephrine reuptake in the central nervous system (15). St. John's wort contains various potentially active compounds; hypericin and hyperforin are thought to be its main active constituents (15) (Table 2).

Efficacy

A meta-analysis of good methodologic quality included 27 randomized, double-blind clinical trials (16). The authors used the Jadad score to evaluate the methodologic quality of the primary studies and found their average quality to be good. Seventeen trials were placebo-controlled and showed efficacy of St. John's wort in mild to moderate depression. Ten compared St. John's wort extracts with standard reference medications and showed apparent equivalence to maprotiline, imipramine, bromazepam, amitriptyline, and diazepam (Table 1). The notion that St. John's wort is efficacious in treating mild to moderate depression is further supported by a review of 6 further randomized clinical trials (17), which did not overlap with the previous meta-analysis (16). The methodologic quality was evaluated by using the Jadad score; 5 trials scored 5 points, and 1 scored 4 points.

Two further high-quality reviews applied stricter inclusion criteria (18, 33), and only 8 (18) and 6 (33) randomized, double-blind clinical trials were summarized (Table 1). All of these studies had been included in the two previous (16, 17) reviews. The methodologic quality of the primary studies was not formally assessed in either of the two later reviews. The authors confirmed that St. John's wort is more effective than placebo in the treatment of mild to moderate depression and is similar in effectiveness to low-dose tricyclic antidepressants.

The perhaps most critical meta-analysis (34) included 14 randomized clinical trials. All of these studies had been included in the two previous (16, 17) reviews. The authors did not formally assess trial quality. The results confirm that St. John's wort extracts were significantly more effective than placebo (relative benefit, 1.9 [CI, 1.2 to 2.8]) and equivalent to tricyclic antidepressants (relative benefit, 1.2 [CI, 1.0 to 1.4]). The authors found evidence of publication bias, which may have led to an overestimation of the effect.

A recent three-armed randomized clinical trial (35) that, in several respects, is the most rigorous trial on the subject to date was not included in the reviews discussed above. In this study, 263 patients with moderate depression received standardized St. John's wort extract, 1050 mg/d; imipramine, 100 mg/d; or placebo for 8 weeks. The results show that St. John's wort was more effective than placebo and equivalent to imipramine in reducing symptoms of depression, as verified by Hamilton Rating Scale for Depression scores.

In summary, St. John's wort appears to be efficacious in the treatment of mild to moderate depression.

Safety

Taken as monotherapy, St. John's wort has an excellent safety profile (**Table 3**) that is clearly superior to that of conventional antidepressants (36). The only potentially serious adverse effects are photosensitization, which is extremely rare, and induction of manic symptoms in predisposed patients (37). However, problems may arise when patients take St. John's wort with other medications. St. John's wort induces a hepatic enzyme through activation of the cytochrome P450 system (38). In addition, it probably activates P-glycoprotein, which further increases the elimination of synthetic drugs (39). Through these mechanisms, St. John's wort can decrease the plasma level of a large range of prescribed drugs (such as anticoagulants, oral contraceptives, and antiviral agents), with possible clinically serious consequences (19, 40, 41). Finally, some evidence indicates that the combination of St. John's wort with selective serotonin reuptake inhibitors can lead to serotonin overload or the serotonin syndrome, particularly in elderly patients (38).

Dosage

About 900 mg of standardized extract (usually standardized to 0.3% hypericin content) has been used in most trials. The clinical effect often takes 2 to 3 weeks to appear. Nonstandardized extracts may be grossly underdosed, and their use should be discouraged. In some European countries, St. John's wort is registered for the treatment of mild to moderate depression; in the United States, it is marketed as a dietary supplement.

GINSENG (*PANAX GINSENG*)

Complex terminology and lack of clear distinction between Siberian or Russian ginseng (*Eleutherococcus senticosus*) and Asian (Chinese or Korean) ginseng

Table 2. **Pharmacologic Profile of Top-Selling Herbal Medicinal Products**

Common Name	Latin Name	Main Active Constituents	Principal Pharmacologic Action
Ginkgo	*Ginkgo biloba*	Ginkgolides, bilobide, flavone glycosides	Multiple cardiovascular and other effects (such as antihypoxic, antiplatelet, and free radical scavenging) that may work together to protect tissue against ischemia
St. John's wort	*Hypericum perforatum L.*	Hypericin, hyperforin, and possibly others	Antidepressant (most likely through serotonin uptake inhibition), antiviral
Ginseng (Asian)	*Panax ginseng*	Ginsenosides, panaxans	Central nervous system stimulation (and suppression), hypertensive, antifatigue, hypoglycemic, antioxidant, anti-inflammatory, anticancer, platelet inhibition, immune stimulant, antineoplastic
Echinacea	*E. angustifolia**, *E. pallida**, *E. purpurea**	Polysaccharides, glycoproteins, alkamides, caffeic acid	Immune system stimulant, antifungal, anti-inflammatory
Saw palmetto	*Serenoa repens, Sabal serrulata*†	Fatty acids, sterols	Inhibits testosterone metabolism; anti-inflammatory
Kava	*Piper methysticum*	Kavalactones	Anxiolytic, muscle relaxant, mood enhancer, analgesic, sedative, antibacterial, platelet inhibitor

* Different species.
† Terms are synonymous.

Table 3. **Safety of Top-Selling Herbal Medicinal Products**

Common Name	Adverse Effects	Interactions	Contraindications*	Cautions†
Ginkgo	Gastrointestinal symptoms, headache, nausea, vomiting	May increase effects of anticoagulants	Concomitant anticoagulation, bleeding disorders	Warn patients to watch for bleeding and report such instances
St. John's wort	Very few when taken alone; nausea and allergic reactions are the most frequent	Probably acts as a hepatic enzyme inducer, thereby decreasing plasma levels of prescribed drugs Serotonin syndrome may result when herb is combined with selective serotonin reuptake inhibitors	Known photohypersensitivity	Do not give to children; watch for interactions with concomitant drug therapies; do not combine with prescription drugs
Ginseng (Asian)	Diarrhea, euphoria, headache, hypertension, hypotension, insomnia (relatively common), mastalgia, nausea, vaginal bleeding	May interact with monoamine oxidase inhibitors, stimulants, hypoglycemic agents, and warfarin	Cardiovascular disease, hypertension, hypotension, diabetes mellitus	"Ginseng abuse syndrome" has been described with prolonged use; do not take for prolonged time at high doses
Echinacea	Anaphylaxis (rare)	In theory, diminishes effects of immunosuppressants	Systemic progressive illness (such as HIV infection, collagen disease, multiple sclerosis, tuberculosis, and autoimmune diseases)	Rebound of immune system after discontinuation is conceivable; do not take for longer than 8 weeks; adulteration of products has been described
Saw palmetto	Constipation, decreased libido, diarrhea, headache, hypertension, nausea, urine retention	May in theory interact with hormonal medication	Women of childbearing age	May cause false-negative result on prostate-specific antigen test; exclude prostate cancer before starting herbal treatment
Kava	Reversible yellowish discoloring of skin, nails, and hair (chronic abuse); visual disturbances; dizziness; stupor; gastrointestinal discomfort; extrapyramidal effects (rare); hepatitis	Potentiates effects of other anxiolytics and alcohol	Children < age 12 y, renal disease, thrombocytopenia, neutropenia	Avoid concomitant use with psychotropic agents and long-term use

* None of these herbal medicinal products should be used in pregnancy or lactation or by people who are allergic to them.
† With all of these herbal medicinal products, instruct patients to report perceived adverse events promptly; data are insufficient on use of herbal medicinal products in infants and children.

(*Panax ginseng*) have generated confusion. The genus *Panax* includes other species, such as American ginseng (*P. quinquefolius*) and Japanese ginseng (*P. japonicus*). Unless stated otherwise, "ginseng" as discussed in this article pertains to *P. ginseng*.

Ginseng has been used for its alleged sedative, hypnotic, demulcent, aphrodisiac, antidepressant, and diuretic activity. It is often recommended to improve stamina, concentration, vigilance, and well-being (31). The pharmacologic activities of *P. ginseng* range from stimulation of the central nervous system to modulation of the immune system and anabolic effects (15). *Panax ginseng* has also been shown to accelerate hepatic lipogenesis and increase glycogen storage (42), which could contribute to an antidiabetic effect. The pharmacologic properties of Siberian ginseng are less well studied but are claimed to be similar to those of *P. ginseng* (15) (Table 2).

Efficacy

A systematic review of adequate quality included 16 randomized, double-blind, placebo-controlled clinical trials of any type of ginseng extract for diverse indications (43) (**Table 1**). Most of the primary studies were of low methodologic quality as judged by the Jadad score, but 6 studies had scores of 4 points. Many trials used healthy volunteers rather than patient samples. Evidence from sound clinical trials did not support the use of ginseng to treat the above-mentioned indications. In addition, a nonsystematic review of animal and human studies of ginseng as an ergogenic aid to physical performance (44) concluded that compelling evidence on the efficacy of ginseng for this indication is lacking.

A recent epidemiologic study (45) of a ginseng-growing region in Korea assessed the nutritional habits of 4634 inhabitants. During 5 years of follow-up, 137 cases of cancer were documented. Persons who regularly consumed fresh Korean ginseng had a significantly reduced risk ratio for cancer of 0.31 (CI, 0.13 to 0.74). Moreover, a dose–response relation between risk for cancer and regular ginseng consumption was noted. Although this study cannot establish a causal relationship, its results seem to warrant further study.

Finally, a recent study showed that 3 g of American ginseng attenuated the postprandial glycemic response to a 25-g oral glucose challenge (46). The effect was seen in nondiabetic persons and in those with type 2 diabetes. The authors caution that American ginseng should be taken with a meal to prevent unintended hypoglycemia in nondiabetic persons.

Safety

Panax ginseng has several relatively serious adverse effects (8, 9, 31, 43), ranging from insomnia, diarrhea, vaginal bleeding, and mastalgia to severe headache, schizophrenia, and the Stevens–Johnson syndrome (**Table 3**). The exact incidence of these adverse effects is unknown but seems to be low. A probable interaction between warfarin and *P. ginseng* has also been observed (47). In that case report, a 47-year-old man whose anticoagulation had been controlled with warfarin experienced a subtherapeutic international normalized ratio of 1.5 after he self-medicated with ginseng at the recommended dose. The quality of many commercial ginseng products (sold as dietary supplements in the United States) is unknown, and adverse reactions might therefore be caused by contaminants.

Dosage

Formal dose-finding studies of ginseng have not been done. Usually, 0.5 to 2 g of dry ginseng root, equivalent to 200 to 600 mg of extract, is used as daily short-term treatment. For continuous administration, the equivalent of 1 g of dry root should not be exceeded. Low-quality products may be contaminated or contain no active ingredient at all; their use should be discouraged, and consumers should be advised to obtain products from reputable sources (**Table 1**).

ECHINACEA (*ECHINACEA* SPECIES)

Commercially available herbal medicines are produced from three species: *Echinacea angustifolia*, *E. pallida*, and *E. purpurea*. Different products use different parts of the plants, mostly roots. Thus, echinacea products vary considerably. Echinacea preparations contain many potentially active ingredients, such as polysaccharides, glycoproteins, alkamides, and flavonoids. No single active constituent has been found (20). Pharmacologic actions include stimulation of the immune system; local anesthesia; and anti-inflammatory, hormonal, antiviral, and free radical–scavenging activities (48) (**Table 2**).

Echinacea has traditionally been used topically and orally for diverse indications, including wound healing, abscesses, burns, eczema, and leg ulcers (9, 31). In vitro experiments suggest that a polysaccharide from *E. purpurea* increases the macrophage production of tumor necrosis factor-α, interleukin-1, and interleukin-B_2 (49). The best-researched indications are treatment and prevention of upper respiratory tract infections.

Efficacy

A Cochrane review (50) summarized 16 randomized clinical trials of echinacea for upper respiratory tract infection (**Table 1**). The methodologic quality of the primary studies, assessed by using the Jadad score, was found to vary; some studies were of good quality. Five trials of common cold prevention that had a placebo-control group tested five different echinacea preparations. Overall, the results were not conclusive. Three prevention trials with control groups that received no treatment suggested a beneficial effect. Of the 8 treatment trials (all placebo controlled), only 2 showed no significant effect in favor of the herbal medicinal products. The authors concluded that to date, evidence is insufficient to recommend a specific echinacea product. They also point out that publication bias may have distorted the results of their review. Thus, echinacea (particularly *E. purpurea*) may be efficacious, but the trial data are weak and inconclusive.

Safety

Adverse effects of echinacea preparations seem rare and consist mainly of allergic reactions, which can be severe (6, 8, 9, 31). The Australian Adverse Drug Reactions Advisory Committee received 11 reports of adverse reactions associated with echinacea between July 1996 and September 1997, including hepatitis (3 cases), asthma (3 cases), rash (1 case), rash with myalgia and nausea (1 case), dizziness with swollen tongue (1 case), and anaphylaxis (1 case) (51). Systematic studies of adverse effects of echinacea have not been done but are needed, given the growing popularity of echinacea. A recent and probably underpowered study found no evidence of adverse pregnancy outcomes after echinacea consumption (21).

Dosage

Dose-finding studies are not available for echinacea. The usual recommended range is 900 to 1000 mg three times daily, equivalent to 6 to 9 mL of pressed juice or 0.75 to 1.5 mL of tincture daily. Some evidence indicates that preparations using juice of *Echinacea purpurea* are the best choice from the myriad commercial products on the market. The quality of the echinacea supplements on the U.S. market varies and is often unsatisfactory (52).

SAW PALMETTO (*SERENOA REPENS*)

The ripe berries of the American dwarf palm (*Serenoa repens* or *Sabal serrulata*) have been traditionally used to treat genitourinary problems; to enhance sperm production, breast size, or libido; and as a mild diuretic (9, 31). Today, saw palmetto is almost exclusively used to treat benign prostatic hyperplasia. The mechanisms of action are not fully understood. Animal experiments have demonstrated antiandrogen activity, and in vitro studies have shown inhibition of 5-α-reductase, the enzyme that converts testosterone to its active metabolite dihydrotestosterone (15). Another relevant pharmacologic action may be inhibition of estrogen receptors in the prostate (53). Reductions in size of the prostate gland have not been uniformly observed clinically.

Efficacy

A systematic review of good methodologic quality analyzed the data from 16 randomized, double-blind clinical trials involving 2939 patients with benign prostatic hyperplasia (54). The methodologic quality was estimated by using the scoring system of Schulz and was deemed to be good on average. Ten trials were placebo controlled and involved monopreparations, 3 used combinations of saw palmetto with other herbal medicinal products versus placebo, 2 compared saw palmetto with finasteride, and 1 compared it with another herbal medicinal product. The results show superiority of saw palmetto over placebo in terms of nocturia and peak urinary flow (**Table 1**) and suggest similar effectiveness compared with finasteride.

The existing trial evidence has been criticized; most of the studies are from Europe, and some have been judged to be of limited value, for instance, because only short-term treatment phases were used (22). A 6-month randomized, controlled trial from the United States recently confirmed that saw palmetto is "a safe and highly desirable option for men with moderately symptomatic benign prostatic hyperplasia" (55).

Thus, good evidence indicates that saw palmetto extract is efficacious short-term (and, probably, medium-term) therapy for symptoms of benign prostatic hyperplasia. In some European countries, saw palmetto is considered first-line therapy for this indication. However, data from large randomized clinical trials are not available.

Safety

Adverse effects of saw palmetto are rare and usually mild (**Table 3**). In all randomized clinical trials in the above-mentioned meta-analysis (54), withdrawal rates (a rough indicator of patient acceptance) were 9.1% for saw palmetto, 11.2% for finasteride, and 7.0% for placebo. No herb–drug interactions have been described.

Dosage

Dose-finding studies of saw palmetto are not available. The dose most often used in clinical trials is 320 mg of a liposterolic extract daily, equivalent to 20 g of crude berries. Treatment usually lasts 3 to 6 months, but no data from rigorous long-term studies are available.

KAVA (*PIPER METHYSTICUM*)

Kava is made from the dried rhizome of the kava plant. It is traditionally used in the South Pacific as a recreational drink. Kava has been used experimentally to attenuate seizures and to treat psychotic states (31). Today, it is mostly used for its anxiolytic effects.

The active ingredient is a family of four pyrones (kavapyrones). Their main pharmacologic properties are a central muscle-relaxing action and an anticonvulsant action (15). The mechanism of the anxiolytic effect is still somewhat controversial; one theory is that kavapyrones enhance γ-aminobutyric acid–binding in the amygdala without acting as direct antagonists at γ-aminobutyric acid receptors (56). Kavapyrones also are powerful strychnine antagonists (15) (**Table 2**).

Efficacy

A recent systematic review and meta-analysis of adequate quality (57) included seven randomized, double-blind, placebo-controlled clinical trials (**Table 1**). The methodologic quality of the primary studies was assessed by using the Jadad score and was found to be variable but good on average; four of the studies scored the maximum of 5 points. Only three of the trials could undergo meta-analysis. The results demonstrated a reduction in Hamilton Rating Scale for Anxiety score in favor of kava, with a weighted mean difference of 9.7 points (CI, 3.5 to 15.8). One trial, not included in the above analysis, compared kava with oxazepam (58). Its results suggested that both medications are similarly efficacious anxiolytics. Collectively, these data suggest that short-term administration of kava is effective in reducing anxiety.

Safety

In randomized clinical trials, the incidence of adverse effects of kava was similar in the experimental and placebo groups (57). Serious adverse effects (Table 3) have been reported but seem to be rare. Two postmarketing surveillance studies involving more than 6000 patients found adverse effects in 2.3% and 1.5% of patients taking 120 to 240 mg of standardized extract (59, 60). Several cases of toxic liver damage were recently associated with kava self-medication (61). When kava is taken concomitantly with other medication that acts on the central nervous system or with alcohol, the effects of kava may be potentiated, leading to a temporal state of impaired vigilance or reduced consciousness; one such case has been reported (62).

Long-term use of kava at high doses is associated with flaky, dry, and yellowish discoloring of the skin; ataxia; hair loss; partial loss of hearing; loss of appetite; and body weight reduction. The dermatologic signs of excessive kava use are known as *kava dermopathy* or *kavaism* (63); they are usually reversible on discontinuation of use (64). Kavaism has thus far been observed only in inhabitants of the South Pacific, who regularly ingest doses at least 100 times higher than those recommended for therapeutic use (15).

Dosage

In randomized clinical trials, doses of kava have ranged from 70 to 240 mg of dried root extract, but the therapeutic window seems to be wide. Dosages up to 330 mg/d have been tested without increasing adverse effect rates (15).

COMMENT

It is encouraging that the current best-selling herbal medicinal products have been examined in randomized clinical trials and systematic reviews of those trials. Some herbal medicines discussed here are associated with seemingly positive risk–benefit profiles: ginkgo (for dementia and intermittent claudication), St. John's wort (as monotherapy for mild to moderate depression), and saw palmetto (for benign prostatic hyperplasia). For ginseng, echinacea, and kava, the evidence is less conclusive.

The discussions in this article are mostly based on systematic reviews. Their quality, as estimated according to published guidelines (23), is generally good or adequate. However, systematic reviews have limitations, particularly in the area of herbal medicine. They are often limited by the quality and quantity of the primary studies. Of note, high-quality systematic reviews may include weak primary studies, and strong primary studies do not guarantee that the quality of a review will be adequate. Moreover, systematic reviews usually assume that herbal medicinal products are comparable (which they are often not), and they are prone to publication bias. These problems can be minimized but can rarely be fully eliminated. Nevertheless, systematic reviews are more likely to arrive at correct conclusions than is any other method, except perhaps megatrials, which have not yet been done in herbal medicine.

Generally speaking, trials of herbal medicinal products have been too few, too small, and too short. The lack of long-term studies is especially unfortunate. Benign prostatic hyperplasia, for instance, clearly requires long-term therapy, but trials of saw palmetto to date are mostly short term (4 to 48 weeks) (22, 54). Thus, the clinician is caught between encouraging results of randomized clinical trials and the relative lack of controlled long-term data. The latter information is needed to make responsible therapeutic decisions.

It is often claimed that the herbal industry cannot sustain the high costs of long-term studies. Because herbal medicinal products cannot usually be patented, the incentives for research investments are much lower than in the pharmaceutical sector. These arguments, however, do not necessarily rule out research investments from the herbal industry. The figures for retail sales show that, in principle, money is not lacking; the challenge is to direct some of it to research. The industry might con-

Table 4. **Recent Publications on Herbal Medicine for a Professional Readership**

Publication	Strengths	Weaknesses
Blumenthal M, ed. The Complete German Commission E Monographs. Austin, TX: American Botanical Council; 1998.	Comprehensive; useful appendices	Not clinically oriented; not referenced; uncritical; not up to date
Blumenthal M, Goldberg A, Brinckmann J, eds. Herbal Medicine. Austin, TX: American Botanical Council; 2000.	Comprehensive; some clinical detail; well referenced	Based on Commission E monographs; in parts uncritical
Boon H, Smith M. The Botanical Pharmacy: The Pharmacology of 47 Common Herbs. Kingston, Ontario, Canada: Quarry Pr; 1999.	Most clinically oriented text available; detailed discussion; most important herbal remedies included; comprehensive references	Even more clinical orientation would be desirable; pocket format might be preferable
Brinker R. Herb Contraindications and Drug Interactions. Sandy, OR: Eclectic Medical Publications; 1998.	Comprehensive; well referenced; good reference text	Not entirely up to date; highly specialized
Cupp MJ. Toxicology and Clinical Pharmacology of Herbal Products. Totowa, NJ: Humana Pr; 2000.	Thorough on toxicology and pharmacology; well referenced	Includes only 28 herbal medicinal products, many of which are not in prevalent use; not clinically oriented
Ernst E, ed. The Desktop Guide to Complementary and Alternative Medicine: An Evidence-Based Approach. Edinburgh: Mosby; 2001.	Concise; clinically oriented; evidence-based; emphasis on safety; up to date; critical	Not comprehensive; low on detail; only key references included
Fetrow CW, Avila JR. Professional's Handbook of Complementary and Alternative Medicines. Springhouse, PA: Springhouse; 1999.	Comprehensive; critical; emphasis on pharmacology; good as a quick reference; useful key references	Not clinically oriented; not fully referenced
Focus on Alternative and Complementary Therapies. London: Pharmaceutical Pr; 2000. Available at www.ex.ac.uk/FACT/	Useful review journal; evidence-based approach; up to date	Not a reference text; deals with topics other than herbal medicine
Mazza G, Oomah BD. Herbs, Botanicals and Teas. Lancaster, UK: Technomic Publishing; 2000.	Thorough reviews; detailed pharmacology	Inconsistent chapters; not clinically oriented; not comprehensive
Newall CA, Anderson LA, Phillipson JD. Herbal Medicines. London: Pharmaceutical Pr; 1996.	Most important herbal remedies included; emphasis on pharmacology; good as a quick reference text; useful key references	Not clinically oriented; not comprehensive; not up to date
PDR for Herbal Medicines. Montvale, NJ: Medical Economics; 1998.	Comprehensive emphasis on pharmacology	Not clinically oriented; based on Commission E monographs; not up to date
WHO Monographs on Selected Medicinal Plants. vol. 1. Geneva: World Health Organization; 1999.	Detailed; emphasis on pharmacology; critical; comprehensive references	Not clinically oriented; not comprehensive; most popular herbal remedies not included in first volume

sider a system to create an association of reputable producers that sets aside a small percentage of each member's profits for the most urgent research projects (65). In the long run, the lack of reliable research data harms the herbal industry as well as the consumer.

The present lack of quality control and standardization of herbal medicinal products is of concern to many experts (66). Whenever such products are independently analyzed, the results show that an alarming proportion is contaminated (for example, by pesticides, herbicides, or heavy metals) or underdosed, or both (52). This situation is obviously unacceptable. It puts the consumer at risk and ultimately operates against the interests of the industry. Regulation of the herbal industry should address these problems by setting quality standards and subsequently branding them as noncompliant manufacturers. Meanwhile, consumers and health care professionals are at a loss when trying to decide which brands of herbal medicines to buy or recommend. One reasonable option is to use brands and extracts that have been tested in clinical trials (66) (**Table 1**).

Herbal medicine is plagued by several further problems. Many vocal and influential individuals insist that clinical research is not a priority. In their view, traditional knowledge and the "test of time" are adequate proof (67, 68). Yet the "test of time" is a notoriously poor guide for establishing the efficacy or safety of traditional therapies (69). The area of herbal medicine, it seems, has been hindered by a tradition of regarding clinical trials as being of secondary importance. However, such investigations, together with adequate postmarketing surveillance studies, are the best (and perhaps the only) way to answer the question of whether herbal medicinal products cause more good than harm.

Attitudes of the general public may be another problem. The present popularity of herbal medicinal products is largely due to the fact that the public perceives them as devoid of adverse effects (70). The media often help to perpetuate this myth (71). All herbal medicinal products are associated with finite risks; those covered in this review are probably safer than many others (6, 72). One issue that will gain relevance as research progresses is the interactions between herbal medicines and prescription drugs (8, 9, 14, 19, 31, 32, 38–41, 72). The potential for such interactions is considerable (14), not least because all herbal medicines contain myriad ingredients (Table 2). It is possible, even likely, that at present we fail to recognize herb–drug interactions simply because we have no knowledge of them.

How should physicians inform themselves about herbal medicinal products? Books on the topic, written mostly for lay people, abound. According to our preliminary evaluation (73, 74), these books represent more of a risk to the health of the reader than a helpful source of knowledge. Fortunately, several recommendable publications for the professional readership have recently emerged (Table 4). Dissemination of objective rather than promotional information, stimulation of rigorous research, and provision of adequate funds (75, 76) are clearly the way ahead and should be in the interest of all parties concerned. Rigorous and systematic evaluation of all herbal medicinal products is urgently needed.

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Therapeutic Angiogenesis for Coronary Artery Disease

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A large body of evidence in animal models of ischemia shows that administration of angiogenic growth factors, either as recombinant protein or by gene transfer, can augment nutrient perfusion through neovascularization. Many cytokines have angiogenic activity; those that have been best studied in animal models and clinical trials are vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). Clinical trials of therapeutic angiogenesis in patients with end-stage coronary artery disease have shown increases in exercise time and reductions in anginal symptoms and have provided objective evidence of improved perfusion and left ventricular function. Larger-scale placebo-controlled trials have been limited to intracoronary and intravenous administration of recombinant protein and have not yet shown significant improvement in exercise time or angina compared with placebo. Larger-scale placebo-controlled studies of gene transfer are in progress.

Clinical studies are required to determine the optimal dose, formulation, route of administration, and combinations of growth factors and the utility of adjunctive endothelial progenitor-cell or stem-cell supplementation, to provide safe and effective therapeutic myocardial angiogenesis. Determination of which growth factors or cells are required to optimize therapeutic neovascularization in an individual patient should be a goal of future research.

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The development of collateral vessels after coronary occlusion has been familiar to clinicians for many years. Collateral vessels appear in relation to a gradually developing high-grade stenosis or occlusion growing at the interface between normal and ischemic tissue. These vessels may be sufficient to preserve wall motion and prevent or reduce ischemia at rest or during stress. Emulation or enhancement of this process by delivery of growth factors to promote neovascularization may therefore be a useful therapeutic strategy.

Folkman (1) identified the therapeutic and pathologic implications of neovascularization due to angiogenic growth factors almost 30 years ago. Work from his laboratory documented the dependence of tumor growth on neovascularization and the role of angiogenic growth factors in this process. More recently, therapeutic angiogenesis (2) has emerged as a complementary strategy to treat vascular insufficiency. Proof of concept in humans was established in severely symptomatic patients with critical limb ischemia (3, 4). Shortly thereafter, clinical investigations were extended to severely symptomatic patients with coronary artery disease unsuitable for revascularization, who are estimated to represent up to 12% of presentations to interventional referral centers (5).

In this review, we discuss the biology of angiogenesis that forms the basis for these clinical studies and summarize what has been learned in clinical trials of therapeutic angiogenesis for myocardial ischemia.

ANGIOGENESIS, VASCULOGENESIS, AND ARTERIOGENESIS

Angiogenesis and vasculogenesis are responsible for the development of the vascular system in the embryo (6) (**Figure 1**). Vasculogenesis is the process of in situ formation of blood vessels from endothelial progenitor cells or angioblasts (7–9), which migrate and fuse with other endothelial progenitor cells and capillaries and differentiate into endothelial cells while forming new vessels in situ (7). In contrast, angiogenesis involves extension of already formed primitive vasculature by sprouting of new capillaries through migration and proliferation of previously differentiated endothelial cells.

Until recently, vasculogenesis was thought to be restricted to embryonic development, whereas angiogenesis (although recognized to occur in the embryo) was considered solely responsible for neovascularization in adults. The paradigm for postnatal neovascularization was revised with the discovery that bone marrow–derived endothelial progenitor cells circulate in peripheral blood (10), home to and incorporate into foci of neovascularization in adult animals (11), increase in number in response to tissue ischemia (12), and augment development of collateral vessels after ex vivo expansion and transplantation (13). These studies established that neovascularization in adults is not restricted to angiogenesis but rather involves both mechanisms observed in the embryo.

A third mechanism that probably contributes to development of collateral vessels is an increase in size and

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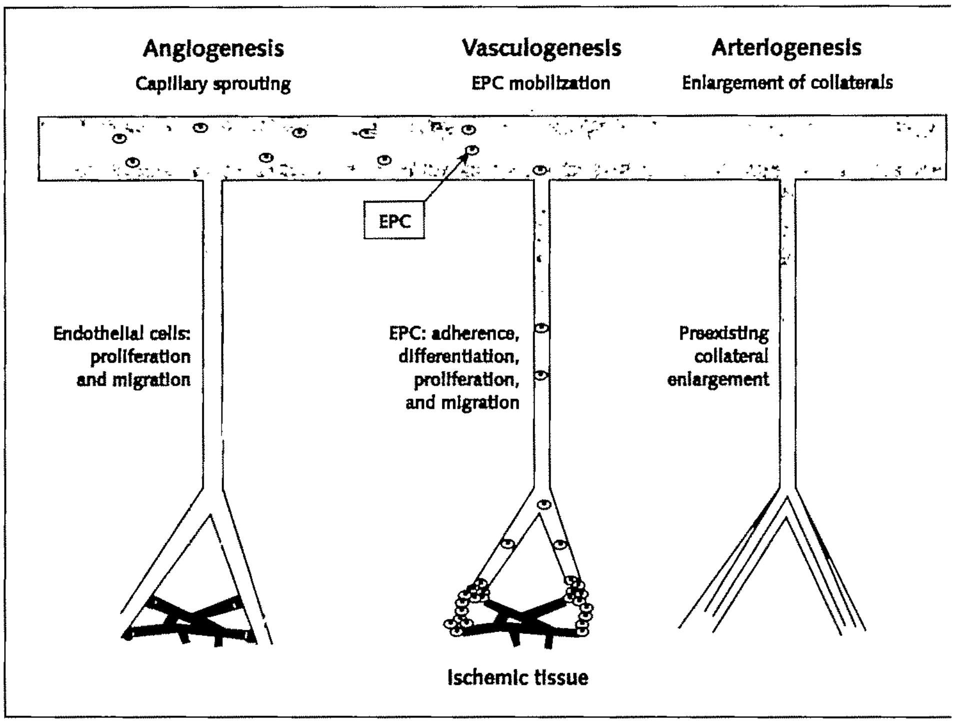
Figure 1. **Mechanisms of neovascularization: angiogenesis, vasculogenesis, and arteriogenesis.**


Angiogenesis
Capillary sprouting
Vasculogenesis
EPC mobilization
Arteriogenesis
Enlargement of collaterals
EPC
Endothelial cells: proliferation and migration
EPC: adherence, differentiation, proliferation, and migration
Preexisting collateral enlargement
Ischemic tissue

Angiogenesis involves capillary sprouting by proliferation and migration of fully differentiated endothelial cells. Vasculogenesis involves bone marrow–derived endothelial progenitor cells (*EPC*), which naturally circulate in peripheral blood, home to areas of ischemia (bottom part of figure), and incorporate into neovascular foci. Arteriogenesis involves enlargement of preexisting collateral vessels.

caliber of preexisting arteriolar collateral connections by remodeling, a process termed *arteriogenesis* (14) (Figure 1). The presence and number of these native collateral vessels varies widely within and among species. When an occlusion occurs, preexisting collateral vessels experience an increase in the velocity of blood flow and a consequent increase in shear stress in the lumen; these factors ultimately contribute to maturation of collateral conduits, particularly medium-sized collateral vessels large enough to be seen on angiography (3, 4, 14).

HYPOXIA AND ANGIOGENIC FACTORS

Hypoxia or ischemia after arterial occlusion is the natural biological stimulus for endogenous angiogenesis (15–19). The effect of hypoxia is mediated at least in part by the binding of the transcription factor hypoxia-inducible factor to the hypoxia response element in the promoter region of the vascular endothelial growth factor (VEGF) gene, thus enhancing its expression (18). Hypoxia also stabilizes messenger RNA encoding VEGF via a sequence in its 3′-untranslated region (15–17, 19).

THE VEGF FAMILY AND VEGF RECEPTORS

The VEGFs are a family of glycoproteins, of which VEGF-1 (also known as VEGF-A) has been studied most extensively in preclinical and clinical trials of therapeutic angiogenesis. The other VEGFs, which share structural homology with VEGF-1, include VEGF-2 (VEGF-C), VEGF-3 (VEGF-B), VEGF-D, VEGF-E, and placental growth factor. Four isoforms of VEGF-1, each the result of alternative splicing, have been identified with 121, 165, 189, and 206 amino acids ($VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{206}$). In a rabbit model of hind-limb ischemia, $VEGF_{121}$, $VEGF_{165}$, and $VEGF_{189}$ had similar angiogenic potency (20). The isoforms differ in their heparin binding capacity: $VEGF_{121}$ does not bind to heparin and is the most soluble, whereas $VEGF_{165}$ and $VEGF_{189}$ bind heparin avidly, remaining more closely bound to either the cell surface or to heparan sulfate in the extracellular matrix. Of note, all VEGF-1 isoforms and other VEGF family members contain a secretory signal sequence that permits their active secretion from intact cells transfected by the VEGF gene.

The principal cellular target of VEGF is the endothelial cell. The common receptor for VEGF-1 and VEGF-2 is KDR or VEGF receptor-2 (VEGFR-2) (21, 22), thought to transduce angiogenic signals. The role of VEGFR-1 (Flt-1) in angiogenesis is controversial (23). Vascular endothelial growth factor receptor-3 (Flt-4) principally mediates lymphangiogenesis (24). Hypoxia upregulates KDR expression and VEGF production by endothelial cells (25–27); this mechanism is consistent with an autocrine loop, which, coupled with proliferation of endothelial cells after this stimulus, may amplify and protract the response to administered VEGF. An important additional role of VEGF is that it increases the number of circulating endothelial progenitor cells; this effect has been documented in mice and humans after VEGF gene transfer (28–30).

FIBROBLAST GROWTH FACTORS

Although cytokines other than VEGF have been shown to promote angiogenesis (31–33), few have been tested in clinical trials (**Table 1**). Apart from VEGF, the fibroblast growth factor (FGF) family has been most widely studied in both experimental animals and patients with advanced coronary disease. Acidic FGF (FGF-1) and basic FGF (FGF-2) are potent endothelial cell mitogens that also serve as ligands for other cell types, including smooth-muscle cells and fibroblasts. Fibroblast growth factors use cell-surface heparan sulfate proteoglycans to facilitate binding to their tyrosine kinase receptors; this binding underlies the rapid extraction of injected FGF from the circulation, particularly in the lungs, and its localization on cells and extracellular matrix, similar to VEGF. Like VEGF, FGFs also stimulate endothelial cell synthesis of proteases, including plasminogen activator and metalloproteinases, that are important for extracellular matrix digestion in the process of angiogenesis (34). Unlike VEGF, the common forms of FGF (FGF-1 and FGF-2) lack a secretory signal sequence; clinical trials of FGF gene transfer have therefore required modification of the FGF gene (35) or use of another member of the FGF gene family with a signal sequence (36, 37).

RATIONALE FOR THERAPEUTIC ANGIOGENESIS IN OCCLUSIVE VASCULAR DISEASE

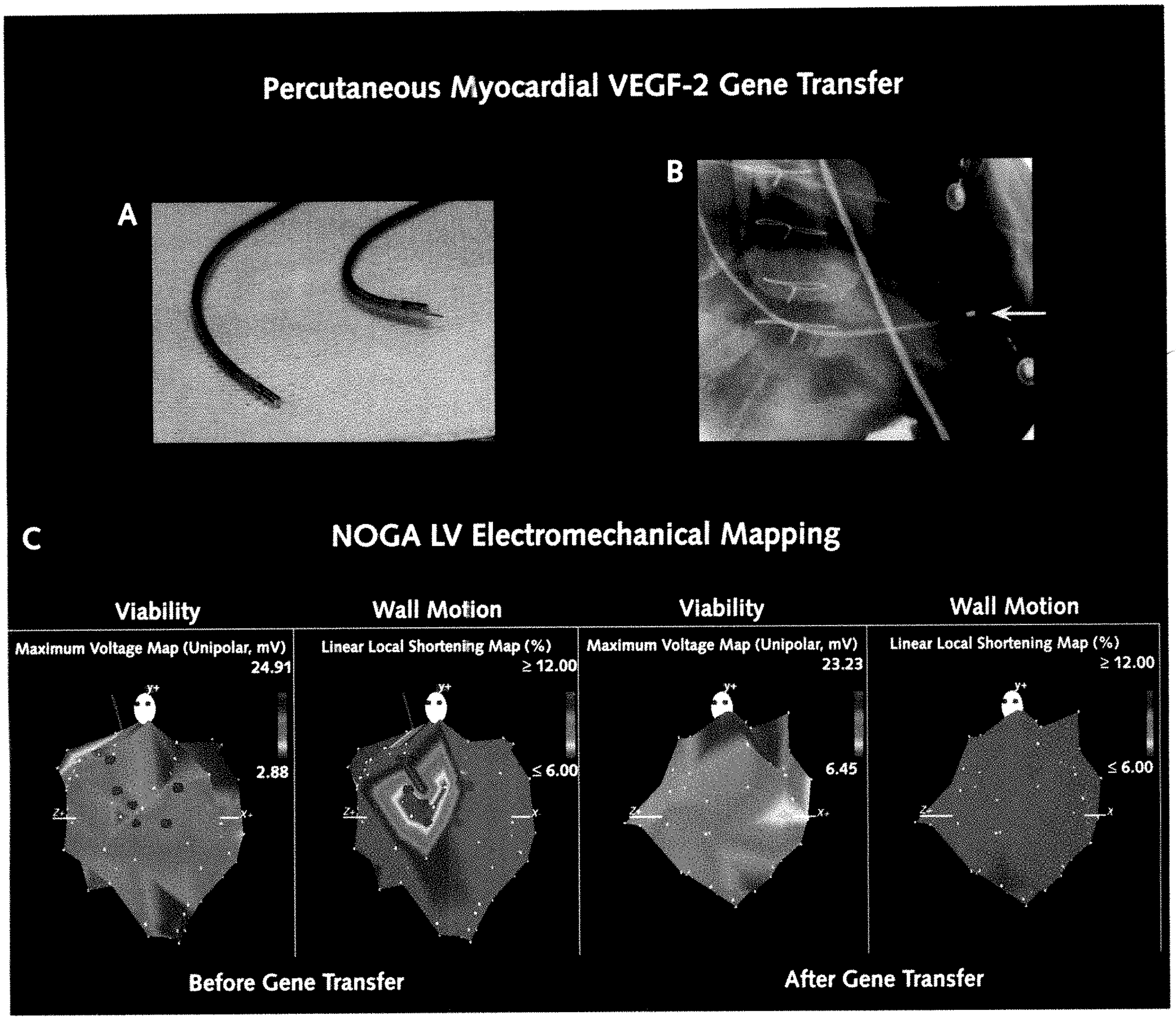
Although ischemia from vascular occlusion upregulates expression of angiogenic growth factors, the fact that patients present with disabling angina indicates such natural compensatory processes are not always sufficient. Two explanations are possible: Production of angiogenic cytokines is inadequate, or the response to them is attenuated. Angiogenesis is impaired in older compared with younger animals (38) secondary to reduced VEGF expression, and similar reductions have been observed in nonobese diabetic (39) and hypercholesterolemic mice (40). Supplementation with VEGF can partially correct these conditions (39, 40). Patients with advanced coronary disease are often older and have diabetes, hypercholesterolemia, or other undetermined characteristics that limit upregulation of angiogenic cytokines by ischemia but may nevertheless respond to administration of exogenous angiogenic cytokines. Greater VEGF production after hypoxia was recently demonstrated in monocytes from patients with angiographically visible collateral vessels compared with those with reduced collateral vessels, suggesting that individual differences in cytokine expression may constitute another basis for variations in collateral development (41).

Table 1. **Angiogenic Cytokines and Genes Used in Clinical Trials of Angiogenesis***

Cytokine	Use in Trials			Properties of Cytokine		
	Protein	Plasmid Human Gene	Adenoviral Vector Gene	Specific for Endothelial Cells	Pleiotropic	Secretory Sequence
$VEGF_{165}$	Yes	Yes		Yes		Yes
$VEGF_{121}$			Yes	Yes		Yes
VEGF-2 (VEGF-C)		Yes		Yes		Yes
Hypoxia-inducible factor-1			Yes			
FGF-1 (acidic FGF)	Yes				Yes	
FGF-1 modified		Yes			Yes	Yes
FGF-2 (basic FGF)	Yes				Yes	
FGF-4			Yes		Yes	Yes

* FGF = fibroblast growth factor; VEGF = vascular endothelial growth factor.

Figure 2. Catheter gene transfer of vascular endothelial growth factor (*VEGF*)-2.


Percutaneous Myocardial VEGF-2 Gene Transfer
A
B
C
NOGA LV Electromechanical Mapping
Viability
Wall Motion
Viability
Wall Motion
Maximum Voltage Map (Unipolar, mV)
24.91
2.88
Linear Local Shortening Map (%)
≥ 12.00
≤ 6.00
Maximum Voltage Map (Unipolar, mV)
23.23
6.45
Linear Local Shortening Map (%)
≥ 12.00
≤ 6.00
Before Gene Transfer
After Gene Transfer

A. The catheter (*left*) and the 27-gauge needle advanced (*right*). **B.** Position of the catheter tip (*arrow*) in the left ventricle. A combination of electromechanical mapping and fluoroscopy is used to guide catheter positioning in the ventricle. **C.** Electromechanical maps before and after VEGF-2 gene transfer. Under "Before Gene Transfer," the left panel ("viability") is the maximum unipolar voltage electrical endocardial map; the changes from green through blue to purple indicate viable hypocontractile areas. The points chosen for gene transfer are marked in brown. The right panel ("wall motion") is the linear local shortening map; an area of hypocontractility is indicated by the red, yellow, green, and blue areas in the anterolateral wall. Surrounding areas have normal contractility (purple). Hypocontractile areas were inferred to be either ischemic or hibernating. The maps labeled "After Gene Transfer," obtained in the same patient 12 weeks after gene transfer, show that viability is preserved (no change in the unipolar voltage map [*left*]), whereas the right-hand map of linear local shortening shows complete normalization of contraction in the previously hypocontractile area, as indicated by the uniform purple color.

Reduced expression of angiogenic cytokines is not the only factor contributing to the heterogeneous response to development of collateral vessels. An age-related reduction in endothelial cell viability was recently demonstrated (38). Endothelial dysfunction accompanies many known coronary risk factors and may reduce endothelial responsiveness to hypoxic stimuli or angiogenic growth factors. Strategies to increase the responsiveness of endothelial cells and increase the production or availability of endothelial progenitor cells are therefore reasonable targets for therapeutic angiogenesis (15, 42, 43).

ANGIOGENIC PROTEIN VERSUS GENE THERAPY

Angiogenic cytokines may be administered as a natural recombinant human protein or by gene transfer. Recombinant protein is a more conventional approach and typically shows a more precise dose–response relationship than does gene transfer. Protein is usually administered systemically and is therefore limited by potential adverse effects of the high plasma concentrations required to achieve adequate myocardial uptake. These adverse effects include hypotension and edema with VEGF (44, 45) and anemia, thrombocytopenia, and renal toxicity with FGF (46, 47). The kinetics of recombinant protein circulation suggest that intravenous delivery is unlikely to result in sufficient myocardial uptake or residence time to achieve important biological effects; intracoronary delivery is an alternative route of parenteral administration (48).

A potentially useful therapeutic regimen would be a single dose that provides a 2- to 3-week increase in angiogenic protein concentration at foci of myocardial ischemia with no increase in systemic levels, to reduce the potential for distant unwanted effects. Current gene therapy strategies can achieve these therapeutic goals. Naked DNA and adenoviral vectors produce only transient transfection, which is suitable for the time frame required for angiogenesis. Whereas intracoronary administration may be sufficient for adenoviral gene transfer (36), naked plasmid DNA requires direct intramuscular injection (49–51) because of degradation by circulating nucleases.

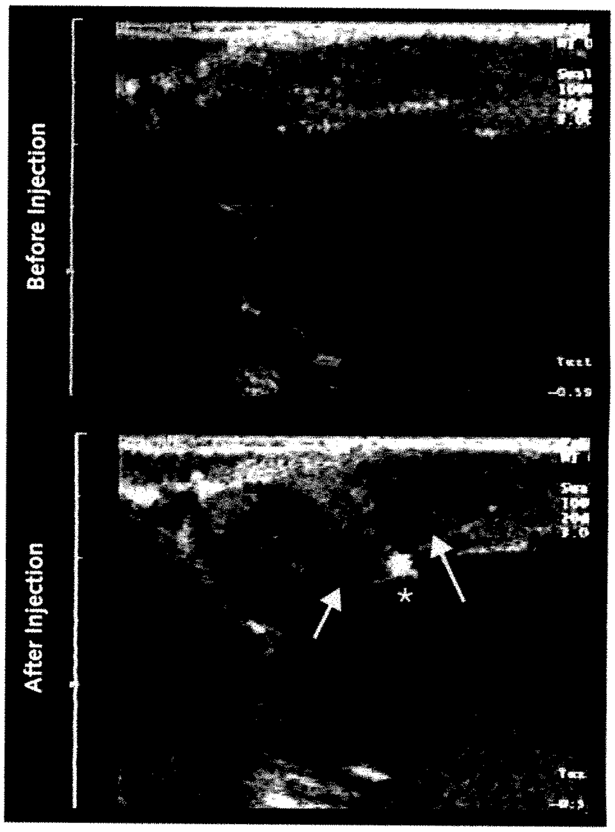
ROUTES OF ADMINISTRATION

Angiogenic cytokines and genes have been administered by diverse routes. Injection sites include intravenous, selective pulmonary artery, left atrium, intracoronary, selective intracoronary, transepicardial intramyocardial or periadventitial during bypass surgery or via thoracotomy, transendocardial intramyocardial by electromechanical catheter, and intrapericardial. Because local delivery of recombinant protein or gene is probably ideal (52), clinical trials have favored the intracoronary (protein or adenovirus) or intramyocardial (naked DNA or adenovirus) route. The transepicardial route carries the attendant risks of surgery; however, these risks are not an issue if transepicardial administration is performed as a part of a coronary bypass procedure, and they may be averted in the future by a catheter-based transendocardial approach (**Figure 2**).

EXPERIMENTAL STUDIES IN ANIMAL MODELS OF MYOCARDIAL ISCHEMIA

The most widely studied animal model of focal myocardial ischemia uses an ameroid constrictor to

Figure 3. **Intramyocardial administration of vascular endothelial growth factor (VEGF) DNA.**



This transepicardial two-dimensional echocardiogram shows the distribution of VEGF DNA solution injected directly into ischemic porcine myocardium. **Top.** The anterolateral free wall (*top*) and the mitral valve plane (*left*), before injection. **Bottom.** A bright needle artifact (*asterisk*) is seen in the anterolateral wall near two echolucent zones (*arrows*) after injection; the echolucency is the result of injected fluid containing the plasmid VEGF DNA.

gradually occlude one coronary artery. The choice of animal is important, because species differ in the number of preexisting arteriolar connections: for example, pigs and rabbits have few, whereas dogs have many. Coronary ligation produces transmural infarction in pigs and smaller, nontransmural infarcts in dogs (53). In these models, angiogenic proteins or genes have been administered by various routes, and their effectiveness has been documented by histologic assessment of the number and size of capillaries or vessels, quantitation of endothelial cell markers, measurement of resting or vasodilated coronary blood flow, angiography, and measurement of left ventricular function at rest or during stress.

Most studies have demonstrated evidence of enhanced angiogenesis after the intervention. Intracoronary injection of FGF-2 for 2 to 28 days increased collateral flow in the dog (54–57), and effects were measurable for up to 5 weeks (58). Central venous administration in the same model was ineffective (57), presumably because of lung sequestration (48). Beneficial effects on collateral flow and left ventricular function were also seen with FGF-2 administration in the pig after single perivascular or intrapericardial doses (59–61). Fibroblast growth factor-1 was ineffective in the dog (62, 63), probably because of rapid inactivation; this can be prevented by altering the structure of FGF-1 (64).

Experience with FGF gene transfer is more limited. Single-dose intramuscular injection of naked DNA encoding FGF-1 and intracoronary adenoviral transfer of the *FGF-5* gene have been shown to improve flow in the rabbit hind limb (35) and porcine myocardium (36), respectively.

The effect of $VEGF_{165}$ protein has been studied in dog and porcine models. Single intracoronary doses were effective in the pig (44, 65), as were a series of two local injections via balloon catheter, 3- or 4-week periadventitial infusions via minipump (65, 66), intramyocardial injection (67), and 28-day intracoronary injections in the dog (68). Intravenous administration was ineffective (67).

Genes encoding $VEGF_{165}$ and $VEGF_{121}$ as well as VEGF-2 have been transfected in several animal studies using naked plasmid DNA or adenoviral vectors. Intramyocardial injection of plasmid DNA encoding $VEGF_{165}$ (69, 70) (**Figure 3**), VEGF-2 (71), or adenovirus encoding $VEGF_{121}$ (72, 73) via thoracotomy in a pig ameroid model improved collateral perfusion and function. Intracoronary adenoviral gene delivery produced much lower gene and VEGF levels in the myocardium and poor localization, which would favor the intramyocardial route (73). Pericardial delivery of adenovirus encoding $VEGF_{165}$ in a dog model did not increase collateral flow (74). Recent studies suggest that catheter-based intramyocardial injection of plasmid $VEGF_{165}$ is effective in the pig (70). This less invasive approach to intramyocardial gene transfer has been shown to achieve suitable gene expression (70, 75–77), and is currently being investigated in a clinical trial of VEGF-2 gene transfer (78) (**Figure 2**).

TRANSLATION OF THERAPEUTIC MYOCARDIAL ANGIOGENESIS FROM BENCH TO BEDSIDE

Species-based differences in myocardial collateralization and the relatively small area of ischemia produced in the pig model underscore the difficulty in applying results from animal models directly to myocardial angiogenesis in humans. In addition, the heart is a difficult organ to access directly for vascular or intramyocardial administration of angiogenic factors, and assessment of neovascularization and blood flow is not trivial. Consequently, we first studied patients with critical limb ischemia. In these patients, the risk–benefit ratio (that is, limb loss versus limb salvage) was considered appropriate for a novel treatment because effective medical therapy is lacking (79) and ischemic skeletal muscle can be accessed easily. Vascular endothelial growth factor plasmid DNA was initially delivered to a patent arterial site in the ischemic limb upstream from the occlusion (3, 80) and subsequently through multiple intramuscular injections using a 27-gauge needle (4, 81). Clinical benefit, including elimination of pain at rest, limb salvage, and healing of ischemic ulcers, was associated with objective findings of improved ankle–brachial index, angiographic evidence of new collateral vessels, and improved blood flow in the leg on magnetic resonance angiography. Having established proof of concept for therapeutic angiogenesis in humans, we and others next sought to extrapolate these findings to patients with myocardial ischemia.

EVALUATING CLINICAL RESULTS OF MYOCARDIAL ANGIOGENESIS

No consensus exists on how best to evaluate the efficacy of therapeutic angiogenesis in patients with coronary disease. Most studies have focused on clinical end

Table 2. **Clinical Studies of Recombinant Proteins for Myocardial Angiogenesis***

Protein	Route of Administration	Dose	Patients	Type of Trial	Active Agent Recipients/Placebo Recipients, *n/n*	Duration of Follow-up
FGF-1 + heparin + fibrin glue	Intramyocardial injection near LAD during CABG, including LIMA	0.01 mg/kg	Three-vessel disease and distal LAD coronary artery disease after LIMA insertion	Phase I	20/20	12 wk to 3 y
FGF-1 + heparin + fibrin glue	Intramyocardial injection at thoracotomy	0.01 mg/kg for each involved vascular bed	Severe angina not treatable by revascularization	Phase I	20/0	6 and 12 wk
FGF-2 + heparin alginate	Periadventitial implantation during CABG	1 or 10 μg of FGF-2 per implant, 10 implants/patient	Nongraftable artery, viable myocardium	Phase I	8/0	3 mo
FGF-2 + heparin alginate	Periadventitial implantation during CABG	10 or 100 μg total dose of FGF-2 or placebo, divided into 10 implants	Nongraftable artery, undergoing CABG, viable myocardium	Phase I	16/8	3 mo (but longer clinical follow-up)
FGF-2	Intravenous injection (14 patients) or intracoronary injection (52 patients)	Incremental administration to total dose of 0.33–48 μg/kg, as two 10-minute 10-mL infusions (2 vascular distributions)	CAD not treatable by revascularization, inducible ischemia	Phase I	66/0	1, 2, and 6 mo
FGF-2	Intracoronary to left main	Incremental protocol, 3–30 μg/kg over 4 minutes	CAD and angina pectoris	Phase I	17/8	1 d to 29 d
FGF-2	Intracoronary injection	0.3, 3.0, or 30 μg/kg total dose, two 10-minute 10-mL infusions (2 distributions)	CAD not treatable by revascularization, reversible perfusion defects	Phase II (FIRST multicenter study)	337 total; allocated in a 3:1 ratio to active agent or placebo	90 d to 6 mo
VEGF$_{165}$	Intracoronary injection	5–167 ng/kg per min, 10 min each artery	Angina, viable underperfused myocardium	Phase I	15/0	30 and 60 d
VEGF$_{165}$	Intravenous injection	17–100 ng/kg per min over 1–4 h	Angina, viable underperfused myocardium not able to be revascularized	Phase I	28/0	60 d
VEGF$_{165}$	Intracoronary injection plus 3 intravenous injections	17 or 50 ng/kg per min intracoronary for 20 min and intravenously for 4 h on days 3, 6, and 9	Angina, viable underperfused myocardium not able to be revascularized	Phase II (VIVA multicenter study)	115/63†	60 d, 120 d, 1 y (in part of cohort only)

* CABG = coronary artery bypass grafting; CAD = coronary artery disease; FGF-2 = fibroblast growth factor-2; FIRST = FGF-2 Initiating Revascularization Support Trial; LAD = left anterior descending; LIMA = left internal mammary artery; LV = left ventricle; MRI = magnetic resonance imaging; SPECT = single-photon emission computed tomography; VEGF = vascular endothelial growth factor; VIVA = Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis.
† The 115 treatment recipients include both those who received the higher dose and those who received the lower dose.

points, including angina class, exercise time, and quality of life; however, these measures are subject to placebo and training effects, which cannot be eliminated in phase I trials, and may limit the power of smaller phase II studies to detect a meaningful difference. Additional objective evaluations are therefore useful to provide evidence of biological effects of therapeutic angiogenesis.

Perfusion imaging with thallium-201 or technetium-99m sestamibi provides objective estimates of relative myocardial blood flow. Improvement of reversible defects after intervention constitutes inferential evidence of angiogenesis (82–85). Positron tomographic measurement of changes in regional coronary flow may be more accurate (86) but are not widely available. Magnetic resonance perfusion imaging may also prove useful for evaluation of angiogenesis (87, 88). Percutaneous catheter-based electromechanical mapping (89, 90) is a novel technique that provides concurrent maps of myo-

Table 2—**Continued**

Outcome	Study Sponsor	Reference
New vessels bypassing distal LAD; increased flow (digital scale) vs. placebo; decreased angina and use of antianginal drugs vs. placebo; similar angiographic improvement at 3 y	No commercial sponsor	93–95
Perfusion on SPECT and exercise capacity improved compared with baseline	No commercial sponsor	107
1 perioperative myocardial infarction in area of implant; all patients free of angina after surgery; variable changes on nuclear perfusion scan	No commercial sponsor	96
2 deaths during surgery and 3 Q-wave myocardial infarctions; less angina, reduced defect size on nuclear perfusion studies with high dose	No commercial sponsor	97
Increased exercise time, quality of life, LV function, nuclear perfusion, and flow on MRI; decreased angina	Chiron	85, 100, 101
Small short-term increase in coronary artery diameter, no change in exercise time or time to ischemia, hypotension up to 3 d, bradycardia and conduction disturbances, transient proteinuria and thrombocytopenia	No commercial sponsor	102
90-day exercise time (65 s vs. 45 s with placebo) and stress nuclear perfusion results did not differ from placebo group; less angina ($P = 0.057$); trend toward improved overall result in older and more symptomatic patients	Chiron	106
Decreased angina in 13 of 15 patients; improved rest nuclear perfusion results with high dose	Genentech	84, 98, 99
Improvement by 2 grades on 40% of rest nuclear perfusion studies and 20% of stress nuclear perfusion studies	Genentech	98
60 d: similar increase in exercise time for active agent and placebo ($\sim$45 s); similar decrease in angina grade and quality of life as placebo; no change on nuclear perfusion or angiography 120 d: high dose decreased angina grade vs. placebo, trend to increased exercise time 1 y: trend toward decreased angina class Placebo group: 3 cases of cancer (including 1 death) and 1 case of worsened retinopathy	Genentech	98, 103–105

cardial viability and endocardial wall motion (**Figure** 2) and identifies foci of hibernating myocardium that can be serially evaluated before and after intervention (83).

Angiographic studies have failed to consistently show evidence of neovascularization, probably because the diameter of most collateral vessels formed after arterial occlusion or therapeutic angiogenesis is smaller than 200 μm (91), a size beyond the resolution of conventional or magnetic resonance angiography. The increased resolution of synchrotron imaging in preclinical angiogenesis studies has confirmed development of these smaller collateral vessels (92).

INITIAL RESULTS OF THERAPEUTIC MYOCARDIAL ANGIOGENESIS IN PATIENTS WITH CORONARY DISEASE

Tables 2 and 3 list completed and ongoing clinical trials of recombinant proteins and genes used for therapeutic myocardial angiogenesis. Patients in these trials

Table 3. **Clinical Studies of Gene Transfer for Myocardial Angiogenesis***

Gene and Vector	Route of Administration	Dose	Patients	Type of Study	Active Agent Recipients/ Placebo Recipients, *n/n*
Plasmid human $VEGF_{165}$	Intramyocardial injection: thoracotomy with TEE control	125 μg, 250 μg, and 500 μg (10 patients each)	CAD not treatable by revascularization, refractory stable angina	Phase I	30/0
Adenoviral vector $VEGF_{121}$	Intramyocardial injection during CABG or thoracotomy	4×10^8 to 4×10^{10} particle units	Ischemic region, not suitable for bypass	Phase I	21/0†
Adenoviral vector $VEGF_{121}$	Intramyocardial injection at thoracotomy, or using video thoracoscopy	4×10^{10} particle units	Severe angina, not ideal for revascularization	Phase I	10/0‡
Plasmid human VEGF-2	Intramyocardial injection via thoracotomy	200 μg, 800 μg, and 2000 μg (10 patients each)	CAD not treatable by revascularization, refractory stable angina	Phase I	30/0
Plasmid human VEGF-2	Intramyocardial injection via electromechanical catheter in LV	200 μg	Refractory stable angina not treatable by revascularization	Phase I	6§
Plasmid human VEGF-2	Intramyocardial injection via electromechanical catheter in LV	200 μg, 800 μg, or 2000 μg‖	Refractory stable angina not treatable by revascularization	Phase I/II multicenter	19 (12/7), allocated in a 2:1 ratio to active treatment at each dose or placebo
Adenoviral vector 5 FGF-4	Intracoronary injection	3.2×10^8 to 10^{11} virus particles; incremental dose	Class 2 or 3 stable angina, ≥1 open vessel with other treatment options	Phase I/II (AGENT study)	60/19, after allocation in a 3:1 ratio

* AGENT = Angiogenic GENe Therapy; CABG = coronary artery bypass grafting; CAD = coronary artery disease; LV = left ventricle; SPECT = single-photon emission computed tomography; TEE = transesophageal echocardiography; VEGF = vascular endothelial growth factor.
† 15 patients had CABG and 6 had thoracotomy.
‡ 6 patients had thoracotomy and 4 had thoracoscopy.
§ 3 controls crossed over to active treatment.
‖ 18 patients (6 in each group) are to receive active treatment, and 9 are to receive placebo. Only 19 of the 27 patients have been enrolled.

generally had severe angina unresponsive to medical therapy and were unsuitable for conventional revascularization. Many studies were small phase I trials with no control groups that were designed primarily to establish safety or to evaluate dose-related effects. Nevertheless, most studies reported encouraging reductions in symptoms, and some described improvement in exercise time or left ventricular perfusion or function. Results of phase I studies, however, must be interpreted with caution. Typically, the number of patients enrolled is relatively small, and in those that lack a control group, a placebo effect cannot be excluded. For studies in which angiogenic therapy is administered in conjunction with bypass surgery, it may be difficult to determine the relative contributions of the angiogenic agent and bypass surgery to the symptomatic response.

CLINICAL STUDIES USING RECOMBINANT PROTEINS

Initial clinical studies of FGF-1 (acidic FGF) (93–95) and FGF-2 (basic FGF) (96, 97) administered recombinant protein intramyocardially or periadventitially with heparin alginate or heparin plus fibrin glue at the time of bypass surgery (**Table 2**). All studies showed some evidence of improvement compared with baseline values or placebo (93–95, 97), although concomitant bypass surgery was an important confounder. In the FGF-2 trials, the high rates of perioperative death and infarction were attributed to advanced coronary disease.

Table 3—Continued

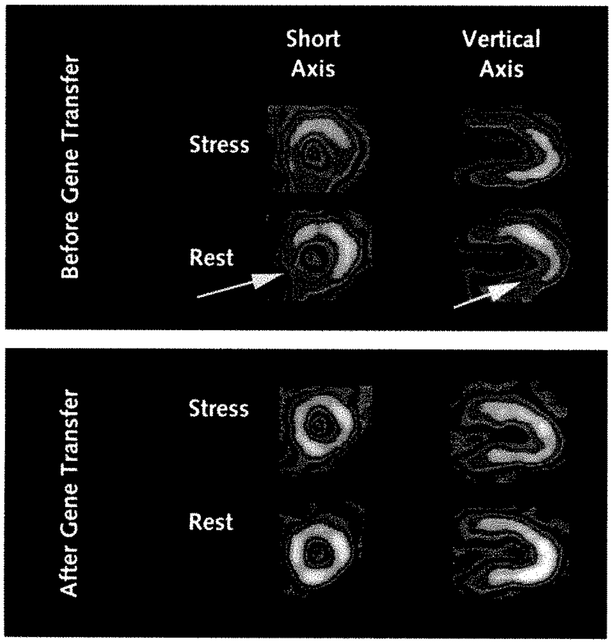
Follow-up	Outcome	Study Sponsor	Reference
2 mo, 6 mo, and 1 y; longer clinical	2 late deaths (4.5 and 28.5 mo), 1 transplantation (13 mo) 60 d: improved results on rest and stress nuclear perfusion, increased function on electromechanical mapping 1 y: less angina and decreased nitroglycerin use (60–3.0 tablets/wk), 98-s increase in exercise time; 2.5-min increase in exercise time to angina	No commercial sponsor	82, 83, 108, 109
30 d	2 perioperative deaths, 1 late death after CABG; decreased angina, increased function on ^{99m}Tc-sestamibi scanning but no change in stress defects on SPECT; increased Rentrop collateral score	Genvec	112
30 d	1 death at 40 d; outcomes not reported	Genvec	113
30, 60, and 90 d; longer clinical	1 perioperative death; 29 patients alive at 1 y 90 d: less angina and nitroglycerin use; >2-min increase in exercise time; improved nuclear perfusion; decreased angina class by ≥2 in 70% of patients; improved function on electromechanical mapping	VGI	110, 111
30, 60, and 90 d; longer clinical	No periprocedural death or myocardial infarction 60 d: less angina and nitroglycerin use 90 d: less nitroglycerin use; decrease in angina from 33 ± 5 to 3 ± 6 episodes/wk in active treatment group and 40 ± 5 to 22 ± 4 episodes/wk in the placebo group ($P < 0.01$); improved results on rest nuclear perfusion; improved function electromechanical mapping	VGI	78
60 and 90 d; longer clinical	No periprocedural death or myocardial infarction; significant reduction in angina class ($P = 0.04$), trend to improvement in exercise time, significant improvement in perfusion of hypoperfused segments on stress image	VGI	114, 115, 116
4 and 12 wk	Nonsignificant increase in treadmill time compared with placebo at 4 (1.3 vs. 0.6 min) and 12 weeks (1.6 vs. 0.9 min); favorable trend if baseline treadmill time or adenoviral titer was low	Collateral Therapeutics	117

Subsequent phase I trials used intravenous or intracoronary $VEGF_{165}$ (84, 98, 99) or FGF-2 (85, 100–102). Most of these studies described significant improvements in exercise time and perfusion and less angina compared with preintervention baseline values and formed the basis for two larger phase II trials, the results of which have been reported but not published.

The Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis (VIVA) study compared two doses of VEGF-1 protein with placebo in 178 patients given a single intracoronary infusion followed by three separate intravenous infusions (98, 103–105). The primary end point, exercise duration at 60 days, was similar in all three groups (approximately 45-second increase over baseline). Angina grade, quality of life, and angiographic or nuclear perfusion at 60 days did not differ significantly among groups. Trends to improvement were seen in the high-dose group at 120 days. Of note, despite exclusion of patients with malignant disease, cancer was diagnosed in 3 patients (including 1 who died) within the 120-day follow-up period; all had been fortuitously assigned to the placebo group.

The FGF-2 Initiating Revascularization Support Trial (FIRST) compared a single intracoronary dose of FGF-2 with placebo in 337 patients. At 90 days (106), FGF did not differ significantly from placebo in the primary end point of exercise time (improvement of 65 vs. 45 seconds; $P > 0.2$) or in results of rest or stress nuclear perfusion. Angina was nonsignificantly less frequent in the FGF group. In post hoc analysis, a significant improvement in exercise time after FGF treatment was seen in patients older than 63 years of age

Figure 4. **Rest and dipyridamole stress single-photon emission computed tomographic sestamibi myocardial perfusion images before (*top*) and 60 days after (*bottom*) vascular endothelial growth factor-1 gene transfer via mini-thoracotomy.**



White and yellow areas indicate maximal radionuclide uptake; red areas indicate impaired uptake. Before therapy, an essentially fixed inferoseptal defect (*arrows*) and a reversible inferolateral defect were observed. After gene transfer, resting perfusion and stress defects in the inferoseptal and inferolateral walls resolved.

(80 seconds vs. 40 seconds in placebo recipients; $P = 0.03$).

The negative results of the VIVA and FIRST studies in terms of primary end points underscore the concern that the pharmacokinetics of recombinant protein administered into the vascular space may lead to inadequate local delivery of angiogenic growth factor to ischemic myocardium, as suggested by studies using labeled ligand (48, 52).

CLINICAL STUDIES USING GENE TRANSFER

Published clinical studies of gene transfer for therapeutic angiogenesis have been limited to phase I dose-escalating, nonrandomized trials (**Table 3**). The largest trial with the longest follow-up involved 30 patients with refractory angina unsuitable for conventional revascularization, who were given naked DNA encoding the VEGF_{165} gene intramyocardially through a mini-thoracotomy (82, 83, 108, 109). An important technical aspect was the use of intraoperative transesophageal echocardiography with test injections to ensure that DNA was not delivered to the left ventricular cavity (118). Intracavitary microbubbles necessitating needle repositioning occurred in 20% of needle placements. At 90 days, weekly nitroglycerin consumption was reduced from 60 tablets/wk to 3.5 tablets/wk, and exercise time increased significantly. Exercise time to angina increased by almost 2 minutes. Improvements in symptoms were maintained at 1 year, when exercise time (increase of 98 seconds) and time to angina (increase of 2.5 minutes) were further improved compared with baseline values.

An important objective evaluation in the final 13 patients was left ventricular electromechanical mapping before and 60 days after gene transfer (83). Foci of electromechanical uncoupling (reduced endocardial shortening with maintained electrical viability) identified preoperatively in all patients improved significantly at 60 days (**Figure 2**). This finding corresponded with improved rest and stress perfusion on single-photon emission computed tomography. Of the 12 patients with rest perfusion defects associated with ischemic endocardial maps, sequential single-photon emission computed tomography (**Figure 4**) demonstrated partial (4 patients [33%]) or complete (5 patients [43%]) resolution of rest defects after gene transfer; this finding is consistent with the idea that these defects constitute foci of hibernating viable myocardium (119–121) that have resumed or improved contractile activity after neovascularization.

Our initial experience with transepicardial intramyocardial naked DNA gene transfer was reproduced in a multicenter study of VEGF-2 gene in 30 patients. Angina frequency and nitroglycerin consumption were decreased and exercise time was increased by more than 2 minutes (unpublished data); improvement in nuclear perfusion and electromechanical maps similar to that described for VEGF_{165} gene transfer (110, 111) was also documented. A single postoperative death occurred 20 hours after gene transfer; the remaining 29 patients were alive at 1 year.

More recently, we completed the first clinical study of percutaneous, catheter-based myocardial gene transfer (78), which was designed to establish the safety and feasibility of nonsurgical needle injection. This single-blind pilot study randomly assigned six patients to gene transfer or a mock procedure; all three patients assigned to the mock procedure required crossover to gene transfer because of persistent symptoms. Anginal episodes decreased similarly in active and control groups at 30 days, suggesting an initial placebo effect (33 ± 5 to 14 ± 5 episodes/wk in the gene transfer group vs. 40 ± 5 to 15 ± 5 episodes/wk in the control group; $P > 0.2$). At 90 days, however, angina frequency increased in the controls, but decreased further in the treatment group (**Table 3**), suggesting that the late reduction in angina was not a placebo effect. Symptomatic improvement was accompanied by improved perfusion and electromechanical function (78, 114). This study served as the basis for a multicenter randomized, double-blind, placebo-controlled trial of catheter-based VEGF-2 gene transfer that has thus far enrolled 19 patients (114). Interim analysis of the 19 patients has revealed significantly improved angina class compared with placebo (115). In more than 1 year of follow-up of 25 patients, no complications and no deaths have been observed after 150 injections of VEGF-2 or placebo.

The combined mortality rate in all four studies of operative or percutaneous VEGF-1 or VEGF-2 gene transfer, including 85 patients with class 3 to 4 angina unsuitable for conventional revascularization, was 3.5% (3 patients) at up to 33 months of follow-up. This rate compares favorably with an average 1-year mortality rate of 11% to 13% among almost 1000 similar patients receiving transmyocardial laser revascularization or continued medical therapy in five contemporary controlled studies (122–126).

Three studies have been done of adenoviral-mediated transfection with $VEGF_{121}$ (112, 113) or FGF-4 (117) gene. In the study of intramyocardial $VEGF_{121}$ gene transfer (112), a first-generation adenoviral vector was given to 15 patients undergoing bypass graft surgery and as sole therapy via mini-thoracotomy in 6 patients. Symptoms improved in both sets of patients, although stress-induced perfusion images were unchanged. The same investigators have since injected adenoviral $VEGF_{121}$ transepicardially by using video-assisted thoracotomy or thoracoscopy in 10 patients; one late death occurred (113).

In the Angiogenic GENe Therapy (AGENT) study, Grines (117) demonstrated the safety of an intracoronary adenovirus vector carrying FGF-4 gene in 79 patients with angina. Nonsignificant increases in treadmill time compared with placebo were observed at 4 and 12 weeks, with favorable trends in certain subgroup analyses.

POTENTIAL RISKS OF INDUCING ANGIOGENESIS

The risks associated with therapeutic angiogenesis include those specific to the growth factor and those generic to promoting angiogenesis. Clinical risks of the former depend on the mode of administration. Parenteral administration of VEGF or FGF-2 protein may produce hypotension (44, 102, 127) because of upregulation of nitric oxide synthesis (128, 129); this complication was not described in preclinical or clinical gene transfer trials. Use of FGF protein has also been associated with proteinuria (47, 102). Evidence of enhanced permeability in humans has been limited to transient leg edema in patients given VEGF gene for critical limb ischemia (45). Angioma formation, observed after protracted or locally supraphysiologic doses of VEGF in mice (130, 131) or rats (132), does not occur with more physiologic VEGF doses (2, 20, 39, 40, 50, 69, 70, 133) and has not been observed in humans.

More generic safety issues are the potential of these agents to stimulate tumor vascularity and growth of occult neoplasms and to exacerbate proliferative or hemorrhagic retinopathy. No in vitro or in vivo data suggest that methods of therapeutic angiogenesis increase the risk for neoplastic growth or metastases, although longer-term follow-up in clinical trials is needed to clarify this matter. More than 100 patients (including nearly one third with diabetes or remote retinopathy) receiving VEGF-1 or VEGF-2 at our institution have undergone serial funduscopic examination by independent retinal specialists before and after gene transfer, with no evidence of new retinopathy at up to 4 years of follow-up (134).

Another potential complication is progressive neointimal thickening due to the effects of administered angiogenic cytokines on vasa vasorum of the artery wall (135). However, five animal (136–140) and four clinical studies (80, 141–143) refute the idea that accelerated atherosclerosis is a likely consequence of administering angiogenic cytokines; rather, animal studies (136–140) have demonstrated that VEGF significantly reduced intimal thickening by accelerating re-endothelialization.

TRANSMYOCARDIAL LASER REVASCULARIZATION

Transmyocardial laser revascularization was first investigated in 1982 (144) as a means of augmenting myocardial blood flow by creating sinusoidal tracts typical of amphibian ventricles. Subsequently, it was suggested that the putative benefit of transmyocardial laser revascularization might result from angiogenesis (145–147), although pathologic studies failed to differentiate whether foci of neovascularization might represent wound healing of laser-induced injury rather than nutrient angiogenesis (148, 149). Moreover, necropsy studies disclosed limited patency of such laser-induced channels (150–152).

Five randomized trials have compared transmyocardial laser revascularization with maximum medical therapy in almost 1000 patients who were not candidates for revascularization (122–126). The 1-year mortality was high (11.5% in transmyocardial laser revascularization recipients and 12.7% in controls). The trials showed reduced angina compared with controls, but changes in treadmill time varied. The effect of transmyocardial laser revascularization on myocardial perfusion was not consistently documented on single-photon emission computed tomography; three of four studies showed no improvement, whereas two uncontrolled studies found no increase in regional blood flow on positron emission tomography (153, 154). Reduction in angina may therefore result from either denervation (154–157) or the placebo effect of thoracotomy. Although initial results of percutaneous catheter–based laser delivery appeared promising (158), a stringent multicenter double-blind placebo-controlled study showed no differences from placebo in angina or exercise duration (159).

CONCLUSIONS

The immediate goal of clinical research in therapeutic myocardial angiogenesis is to demonstrate efficacy in larger scale, placebo-controlled trials. Evaluation of therapies designed to promote collateral development would benefit from improvements in imaging technologies to produce high-resolution images of vessels smaller than 200 μm in diameter (92), which is not possible with current angiography. It remains to be demonstrated that optimized tissue exposure to growth factor can be achieved with single or multiple injections of recombinant protein; consequently, certain groups are investigating sustained-release formulations (Ferrara N. Personal communication). In contrast, sustained release over 2 to 4 weeks is an inherent feature of gene transfer (50, 160), and may constitute an advantage. Further studies will be required to confirm preliminary suggestions that levels and duration of gene expression with plasmid DNA are sufficient to achieve therapeutic angiogenesis while avoiding adverse effects and to optimize the choice, dose, and route of administration of angiogenic growth factor. Similarly, clinical trials will be required to test combinations of growth factors (161, 162) in an attempt to reproduce the cascade evolved by nature to elaborate vascular networks.

Because the numbers of endothelial cells capable of responding to angiogenic cytokine replacement may limit the ultimate magnitude of therapeutic angiogenesis (15, 38–40, 42, 163, 164), a strategy of administering expanded populations of endothelial progenitors harvested from the patient's own circulating blood appears to be promising (13, 165). Complementary strategies supplying not only the growth factor but also the cells responsive to the ligand may be required for optimally robust vascularity. Implicit in this approach is the development of methods to identify which patients are likely to have inadequate cytokine (41) or cellular responses to ischemia, so that therapeutic angiogenesis may be tailored and targeted appropriately.

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Caring for Patients at the End of Life: Reflections after 12 Years of Practice

Richard A. Parker, MD

Physicians have the privilege and authority to assist patients and their families at the end of life. Regardless of diagnosis, commonalities occur in the dying process, and palliative care benefits patients and families. This perspective chronicles my experience over 12 years caring for 95 patients at the end of life, illustrated in part with six vignettes. I describe interactions with families, discuss logistic issues around dying, examine the do-not-resuscitate issue, and highlight experiences with home visits. I also touch on how I communicate with the family after a death. I hope to express the significance of what I have learned while assisting patients and families at this critical juncture.

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Quality end-of-life care benefits patients, families, and physicians. Fear of abandonment, indignity, pain, discomfort, and the unknown trouble most of us when we contemplate dying and death. In my primary care practice at an urban teaching hospital, I have cared for 95 patients who have died over the past 12 years. I believe that relationships among the patient, physician, and family built over time usually allow a "good death" and almost always prevent unwarranted resuscitation, futile interventions, and unnecessary suffering. I view the end of life not as a failure for the patient or physician but as a valuable opportunity for growth, insight, and closure.

Death is the bookend experience to birth, yet we are far from our agrarian roots, where this cycle of birth and death was a normal part of daily life. Our society celebrates and worships birth but flees death as if it were avoidable. As the only person empowered to directly assist in navigating life's end, the physician, with skill and caring, must bring meaning and solace to patients and families as death looms.

My experience suggests that the varied circumstances leading to death culminate in a single pathway, with patients and families experiencing a reasonably predictable set of emotions, fears, and conflicts. I find that proper emotional and physical support affords patients the opportunity to reflect and share with family and friends in a profound way. Moreover, I have learned that good palliative care usually circumvents requests for euthanasia or assisted suicide. To perform end-of-life care, I have had to explore my feelings about death so that I could be open to patients' anxieties, ideas, and questions. In my world view, I accept dying and death as part of the "package deal" of living. This acceptance of the inevitability of death shapes the construct from which I listen to my patients.

VIGNETTES

These vignettes demonstrate the unique circumstances of each dying person and suggest that a flexible approach to end-of-life care is required.

Ms. N.

Ms. N. was a 22-year-old woman with spina bifida complicated by osteomyelitis and paraplegia. Often infected, she spent about 4 months each year in the hospital. Complaining rarely and usually exhibiting a lovely smile, she captured my heart and the hearts of the nurses. I came to know her parents well, and her grandmother even better, since she spent every night in the hospital room on an uncomfortable cot. In the days before Ms. N. died, she became blind and incoherent. On her last night, the nurses called me when she was about to stop breathing. Everyone was crying. I felt my own tears and a lump in my throat. As the attending physician, should I cry? No one had taught me what to do in that situation. I attended Ms. N.'s wake and viewed her in an open casket in a dark funeral home. She looked beautiful and peaceful, adorned with a red rose. Caring for Ms. N. was draining and uplifting.

Dr. K.

Dr. K. was a 47-year-old physician with AIDS. He lived alone with his dog and requested inpatient hospice care after he could not look after himself. As his systemic cytomegalovirus infection, refractory diarrhea, and weight loss progressed, he asked to be admitted to the new palliative care unit. Dr. K. did not like the room, the food, the staff, the medications, or anything about the place. I dreaded visiting him daily and would brace myself for his withering complaints. Already angry about dying and losing his independence, he felt that this "incarceration" was the ultimate indignity. After several weeks, he decided to leave the unit. He cobbled together a schedule for friends to care for him, and he died peacefully at home with the assistance of hospice. His experience illustrated the need for flexibility; I accommodated his change of plans.

Ms. T.

A 73-year-old heavy smoker with severe emphysema, Ms. T. was skinny and spoke with pursed lips. I traveled to her charming, shuttered old house in Boston, where she lived with her lap dog, housekeeper, and two unmarried sisters. In her last year, Ms. T. was rushed to the hospital several times for respiratory failure. She was intubated and always squeaked through. The time came, however, when it seemed that she would not survive another intensive care unit stay. Her Catholic beliefs forbade her to refuse life-sustaining treatment; the idea of do not resuscitate, or DNR, was anathema to her. Frustrated, I felt she suffered needlessly, both physically and emotionally, but I did not feel that I should impose my beliefs on her. One day, another patient, Sister M., came in for a physical examination, and I asked her for advice about this dilemma. She offered to visit Ms. T. in her hospital room, and as a result, Ms. T.'s priest became involved and gave her permission to "let go." Ms. T. died peacefully that month. Spirituality plays a central role in the lives of many people, and I might have helped her sooner by finding an interdisciplinary team to address this.

Mr. S.

Mr. S. was a widely respected artist dying of metastatic pancreatic cancer at home with hospice services. Miserable with pain, he hated to rely on others. Mr. S. asked me to admit him for a brief hospital stay to control the pain. On admission, I wrote a modest morphine order to make him comfortable. With his family present, he said emphatically, "Give me enough morphine to make me comfortable—I don't care if I am not alert or even conscious." A nurse thought my morphine order was excessive and asked me to rescind it. I declined. The nurse did not understand that prior doses of morphine had created tolerance, protecting him against respiratory depression. She called the hospital lawyers; they insisted on meeting with me.

On a hot Friday afternoon, the nurses, resident physicians, two hospital lawyers, and I discussed Mr. S. Our opinions differed radically—was this medically acceptable comfort care or assisted suicide? Some did not accept my explanation of "double effect"—palliative doses of morphine possibly hastening but not intended to cause death. Because we could not agree, I insisted that the lawyers come to Mr. S.'s room and explain why he could not receive this dose of morphine. The lawyers presented their case in a straightforward, anxious manner. Flanked by his wife and daughter, Mr. S., gaunt but with his dignity intact, sat straight up in bed as if holding court and announced, "We're leaving." They packed up and left that evening. A week later, he died peacefully at home. Mores have changed since then, and the staff and I probably would not have such differing opinions today. At the time, while attempting to protect the interest of my patient, I felt pitted against the hospital.

Mr. E.

Mr. E., a 60-year-old man, did not look a day older than 45. He was incredibly fit, tanned, and very opinionated about his health. Disparate symptoms brought him to my office frequently and, to our surprise, a stress test and angiography revealed significant coronary disease. He adopted a strict low-cholesterol diet supplemented with herbs, seeds, and oils. He began to control his emotions with behavioral meditation techniques and group therapy. One summer day, he angrily disagreed with the carpenter at his home about some aspect of renovations. During the shouting match, he dropped to the ground and died. We had never discussed DNR status.

Mr. B.

Mr. B. was the only patient who, along with his family, insisted on "doing everything" to the very end, despite my admonition that he would not survive attempts at resuscitation. At age 94, he suffered a myocardial infarction complicated by congestive heart failure. I doubted he could be weaned off the ventilator with any quality of life, and I suggested a DNR status. His elderly wife and son (also my patients) believed that he would persevere and recover. Because he was "a fighter," his family remained certain that Mr. B. would have chosen this course for himself. When the predictable terminal ventricular fibrillation occurred, his frail, depleted body was repeatedly shocked to the dismay of the nurses and residents. I silently debated how forcefully I should assert my opinion to desist from such futile resuscitation versus allowing patient and family autonomy to rule the day.

OBSERVATIONS

At the time of death, DNR orders were in place for 78 of 95 patients under my care, including all 32 patients with cancer, all 8 patients with congestive heart failure, and all 7 patients with AIDS. These orders were in place for all patients dying in the hospital, except for Mr. B., who insisted on resuscitation, and 1 patient who had cardiac arrest during cardiac catheterization. Of 78 patients with DNR orders, 40 died at home, 34 died in the hospital, 3 died in community hospices, and 1 died in a nursing home.

DNR Status

Contrary to popular belief, I find that discussing end-of-life issues rarely takes a lot of time. Most chronically ill patients have considered dying and issues of resuscitation, and they are usually prepared (and relieved) to discuss it. In my experience, very few patients and their families have declined to discuss dying.

Although physicians are exhorted to discuss end-of-life issues with healthy patients, I find I can address the issue more naturally when the patient is significantly ill and more likely to be thinking about dying. I experienced only one situation in which an advance directive was useful in resolving a family conflict. I favor advance directives as a stimulus for patients and families to clarify their feelings rather than as a tool needed at the end of life.

Hastened Death

In my experience, patients rarely ask for euthanasia or assistance with suicide, although many think about it. Only one patient in this series made an explicit request. This elderly man with life-long depression and escalating cancer symptoms allowed me to speak directly with his psychiatrist. Changes in his antidepressant regimen and more frequent visits with his psychiatrist and me diminished his wish to immediately end his life.

Many patients or their family members have expressed anxiety about potential physical suffering, such as intractable pain or suffocating. They have benefited most from specific information about how morphine, lorazepam, and other medications alleviate these symptoms. Although I emphasize that dying patients can usually be kept comfortable, I warn patients to expect some pain and discomfort and explain the tradeoff that may occur between pain control and lucidity.

Logistics

Logistic challenges present formidable barriers to end-of-life care. A patient may wish to die at home, but family members may be unable to handle the physical or emotional burdens of such care. Financial and insurance limitations may influence decisions about staying at home versus being in a freestanding hospice or hospital setting. The process works best when physicians collaborate with the hospice nurses, family, and social worker.

If a family chooses to avoid a home death, facilitating transfer to an inpatient or freestanding hospice can be invaluable. An inpatient hospice must also be flexible by allowing a patient to come in for "respite" care and then to return home to die (as in Dr. K.'s case).

Home Visit

For patients who have chosen to die at home, I visit at least once if they live within a reasonable distance from the office. It gives me the chance to assess the patient's physical and emotional status and the effects of medications. For the family, the visit reinforces my commitment to the patient's care and comfort and helps diminish fear of abandonment and isolation. Invariably a moving experience for me, this seems extremely valuable to patients and families.

Often, a patient will ask, "What is dying like?" As physicians, we often forget that many people have never witnessed someone dying and may harbor a variety of misconceptions. I explain that disordered breathing accompanied by odd sounds and gasps is normal and does not signify pain. I liken the process to a clock no longer wound every day that gradually runs out of energy. When the clock runs down, all the parts stop. This simple explanation reassures most people, and a calm demeanor reduces anxiety.

In this fragile and vulnerable time, the patient may express regrets about family relationships or concerns about how a spouse or child will fare. Often, family members are also my patients, and this visit enhances our bonds. How wonderful to sit with the family in the kitchen having a cup of coffee and sharing memories of the person who is slipping away. Distant from the headaches of managed care paperwork, incessant messages, and telephone calls in the office, such moments epitomize the essence of the patient–physician relationship. I believe that a home visit at the end of life should be required in medical school and residency curricula. I hope that clinicians will incorporate this signal event into their practices.

Death

Frequent communication with family members in the final 1 or 2 days is vital. An extra telephone call to the home or an extra visit to the hospital room greatly reassures anxious and fatigued family members. Medications often need adjustment several times per day. For logistic reasons, I have been present at the moment of death more often in the hospital than in the home. Sometimes being in the room with the family feels right; other times, waiting nearby and being available to the family immediately after the death seems more appropriate. It can be a searing time, and I need to remain near the family.

After Death

I always write a letter or call the family to express my sadness and some of the joy I had serving as the physician. Often a family member may have lingering questions about why certain events happened or may express guilt about a role they did or did not play. A brief conversation is helpful. On a few occasions, when I felt particularly close to a patient and family, I attended the funeral and always benefited from that powerful experience. On these occasions, the families seemed to appreciate my presence; physicians need closure too. Regardless of denomination, the service welcomes and heals us, bringing home the gravity and importance of our work.

CONCLUSION

Daily, physicians strive to comfort, diagnose, treat, cure, and extend life with quality. Yet, we must recognize when to shift to palliative care. Patients expect, hope, and trust that their physicians are versed in dealing with end-of-life issues, but physicians need to learn and practice these skills. How ironic it is that as physicians, we rarely talk about dying amongst ourselves—even though our patients expect us to be expert in such care.

Keeping a record of all my patients who have died helps me to honor their memory and reminds me of the lessons they have taught me. Collecting this history also sheds light on issues deserving improvement, such as instituting a home visit near the end of life. Regardless of the inexorable march of technology, birth and death will continue to bound our existence. Our society awards to physicians the authority and privilege of caring for people at the end of life. I have learned that caring for patients in the last chapter of their lives is the most important part of my job.

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EDITORIAL

Are Long-Term Very Low Doses of Prednisone for Patients with Rheumatoid Arthritis as Helpful as High Doses Are Harmful?

Treatment of rheumatoid arthritis with corticosteroids has evoked controversy for half a century. Extremely successful initial clinical results (1) led to the awarding of the 1950 Nobel Prize in Medicine to Kendall, Reichstein, and Hench. Some early clinical trials indicated that corticosteroids had "disease-modifying" properties in retarding radiographic progression (2). However, it was soon recognized that severe toxicities associated with the long-term pharmacologic doses of prednisone used at that time (20 to 40 mg) almost invariably outweighed any benefits (3). By the late 1950s, clinicians were taught that while occasional corticosteroids might be needed for acute life-threatening rheumatoid vasculitis or severe disease flares, long-term corticosteroid treatment had no place in the management of most patients with rheumatoid arthritis.

A reassessment began during the 1980s, based in part on recognition of severe long-term outcomes of rheumatoid arthritis (4, 5). A small clinical trial indicated a nonsignificant advantage with 5 mg of prednisone versus placebo (6). A more recent clinical trial reported by Kirwan (7) has confirmed that corticosteroid dosages as low as 7.5 mg/d for 2 years have "disease-modifying" properties in slowing radiographic progression. Nonetheless, corticosteroids continue to be regarded generally as temporary "bridge" therapy rather than as a long-term therapy in rheumatoid arthritis, particularly because high doses have been associated with higher mortality rates (8, 9) and doses as low as 10 mg have been associated with bone loss (10).

Clinical practice and the medical literature are not always congruent. In 1990, 75% of 532 patients monitored in seven U.S. private practices were taking low-dose corticosteroids (11). Patients who receive corticosteroids have more severe disease, confounding retrospective assessment of their long-term risks. Furthermore, patients in earlier studies (8, 9) had received high corticosteroid doses at least some of the time.

In this issue, van Everdingen and coworkers, of Uterecht, the Netherlands, present new insights concerning corticosteroid therapy for rheumatoid arthritis (12). The authors randomly assigned 41 patients to placebo and 40 patients to treatment with prednisone, 10 mg/d, over 2 years. The prednisone group showed significantly greater clinical improvement than the placebo group, particularly over the first 6 months, with significantly lower radiographic progression, indicating "disease modification." However, the prednisone group also experienced more adverse events, including an average increase of 3 kg in body weight versus no increase, hyperglycemia in 2 versus 1 patient, and new vertebral fractures in 5 versus 2 patients compared with the placebo group. Corticosteroid therapy, therefore, led to both greater efficacy and more adverse events, although most patients experienced no adverse events over 2 years.

The elegantly designed and well-executed Utrecht study presents a unique opportunity to evaluate benefits and risks of corticosteroids independent of other therapies, a clinical setting that is unlikely to recur. The authors recognize that the design of this study, which was performed from 1992 to 1995, would not be acceptable today because of logistic and ethical considerations (13), including evidence that additional disease-modifying antirheumatic drugs appeared to be required to slow progression of joint damage optimally (14). Their data suggest that the traditional proscription against the long-term use of corticosteroids in rheumatoid arthritis may not be the best advice for all patients. Nonetheless, as with all research advances, the Utrecht study raises several questions that require further investigation.

First, what is meant by "low-dose" prednisone? A dosage of 10 mg/d may be regarded as "intermediate" or even "high" by some clinicians, including ourselves. In 146 of 152 patients with rheumatoid arthritis who took corticosteroids over 1 to 20 years (median, 6.7 years) under care of the first author of this editorial between 1998 and 2001, the median prednisone dose was 4 mg, in 1-mg tablets. Only 10% of patients were taking more than 8 mg/d, which is regarded as a "high" dose in our clinic. The current initial prednisone dosage in most patients is 3 mg/d. The prevalence of hypertension, cataracts, or diabetes in these patients did not differ from that seen in a cohort of patients with early rheumatoid arthritis (Sokka T, Pincus T. In preparation). However, thinning and bruising of the skin are common, and questions of skeletal maintenance remain unresolved because formal bone density studies are not yet available in all patients.

There seem to be major differences in outcomes of long-term treatment with corticosteroids in low versus high doses over long (or short) periods (15, 16). High-dose corticosteroids are unacceptable in most situations, while low doses may be tolerable or even desirable in some patients. An analogy understood by patients is that a little corticosteroid, like a glass of wine, may benefit many people, whereas a high dose of corticosteroid, like a bottle of wine, is harmful to all. A physiologic, rather than pharmacologic, dose of corticosteroids may address pathogenetic mechanisms of inadequate adrenocorticotrophin hormone responses to corticotrophin-releasing hormone (17).

Prednisone, in doses of 5 mg or less, appears to provide considerable clinical benefit to many, if not most, patients with rheumatoid arthritis and seems well tolerated in many patients. Fewer than 10% to 20% of patients appear to need doses of 10 mg or more. However, most patients continue to take ongoing low-dose prednisone treatment to control symptoms; this often results in lower long-term total corticosteroid dosage than recurrent high doses and discontinuation. Prevention of long-term damage in rheumatoid arthritis appears to require ongoing, indefinite drug treatment (rather than "bridge therapy"), as is the case with most other chronic diseases such as hypertension and diabetes, because even excellent new disease-modifying drugs do not address the fundamental pathogenetic dysregulation. It remains to be determined whether long-term low-dose corticosteroids should be a component of a "preventive" strategy (14) because many repsected clinicians remain opposed to any corticosteroid use (18).

A second question is, Does low-dose prednisone in doses of 5 mg or less have disease-modifying properties beyond symptomatic relief? Controlled clinical trials may contribute valuable data. The problem is confounded by the fact that 1-mg prednisone tablets are not available in many countries and, if available, are more expensive than 5-mg tablets (because of prescription volume). It may be desirable that 1-mg prednisone tablets be made more widely available, even if only to relieve symptoms at low cost.

A third question emerges: Is the "tradeoff" of less joint damage versus skin changes and possible long-term adverse effects of very-low-dose prednisone appropriate for patients with rheumatoid arthritis? In theory, answers should emerge from randomized, controlled clinical trials, such as the Utrecht study. However, clinical trials in rheumatoid arthritis (and other chronic diseases) generally cannot provide definitive information, in part because they are too short term and ignore individual variation (19). Patients with lymphoma may receive high doses of corticosteroids with little questioning of adverse events, while use of *any* corticosteroid in rheumatoid arthritis had been proscribed for decades despite evidence that some patients had a prognosis for death comparable to that of patients with stage IV Hodgkin disease (20). Estimates of benefits and risks of corticosteroids in rheumatoid arthritis will vary among individual patients and individual clinicians, affected by variables such as age, disease severity, comorbid conditions, skin fragility, and intrinsic assessment of risks of drugs and disease. The physician can hope to provide the best information to assist the individual patient in making an informed decision.

Finally, it is commendable that the Utrecht group has chosen to reanalyze an old therapy that has been available for more than 50 years. Most clinical trials of rheumatoid arthritis in the United States (and elsewhere) involve new therapies, such as leflunomide, etanercept, infliximab, and anakinra, used singly and in combination (14), and are sponsored by pharmaceutical companies. Few formal studies are performed to develop improved clinical usage of "old" therapies, particularly the most widely used drugs—low-dose corticosteroids and low-dose methotrexate. New drugs contribute exciting advances to modern treatment. Nonetheless, further clinical trials and long-term observational studies of old therapies will enhance these advances to improve the lives of people with rheumatoid arthritis.

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Pharmacist Scope of Practice

American College of Physicians–American Society of Internal Medicine*

This paper explores the increased scope of practice of U.S. pharmacists. It presents background information on the pharmacy profession and outlines how the medical profession can work with pharmacists to enhance patient safety and quality of care. The paper calls for further research on the effects of pharmacy automation and the move to the Doctor of Pharmacy degree on pharmacy practice. Other positions include support for patient education and hospital rounds, opposition to independent pharmacist prescriptive privileges and initiation of drug therapy, increased use of the pharmacist as immunizer (as allowed by state law), and continued support for the American College of Physicians–American Society of Internal Medicine 1990 therapeutic substitution position.

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Pharmacists, as well as other nonphysician health care providers in the United States, are advocating for increased scope of practice. Their efforts have been successful in several cases. As of early 1999, 24 U.S. states allowed some type of collaborative practice agreement in which physicians delegate patient management responsibilities to pharmacists. The responsibilities range from refill approvals to modification or initiation of patient medication regimens (1) (Appendix).

In addition to broad collaborative agreements. pharmacists are focusing on many other individual practice issues, including prescriptive privileges, disease management, immunization, collaborative drug therapy, laboratory testing and analysis, and patient education. These issues continue to appear in our state legislatures. More than 30 states are expected to consider bills this year to grant prescriptive or independent practice rights to nonphysicians, including pharmacists (1).

THE PHARMACY PROFESSION

Pharmacists practice in various settings, including community pharmacies, hospitals, long-term care facilities, the pharmaceutical industry, mail service, managed care, and government (2). State law regulates the practice of pharmacy, including licensure. To practice pharmacy in any state, a pharmacist must become a registered pharmacist (RPh), also known as a licensed pharmacist. Although requirements vary by state, a licensed pharmacist must, generally, have graduated from an accredited college of pharmacy, participated in a residency or internship program, and passed the National Association of Boards of Pharmacy Licensing Examination (NABPLEX) (3). In addition, most states require completion of continuing education courses to maintain licensure (3).

All registered pharmacists must hold at least a Bachelor of Science degree in pharmacy, but in 1992, a majority of the nation's pharmacy schools voted to change the only professional degree in pharmacy to the Doctor of Pharmacy (PharmD) degree (4). Programs that confer the PharmD degree require 4 years of education beyond the minimum 2 years of prepharmacy study. Professional courses required for this degree include pharmacognosy, pharmacology, pharmaceutical chemistry, pharmaceutics, clinical pharmacy, drug information, and pharmacy administration.

In 1976, the American Pharmaceutical Association established the Board of Pharmaceutical Specialties to recognize specialty areas of pharmacy practice. Board certification is a voluntary process for currently licensed pharmacists. The four basic requirements for board certification are an entry-level pharmacy degree, an active pharmacy license, defined additional training and experience in a specialty, and passing the specialty qualifying examination. The Board of Pharmaceutical Specialties currently recognizes five specialty areas (5): 1) nuclear pharmacy (recognized since 1978)—specialists seek to improve and promote the public's health through the

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safe and effective use of radioactive drugs for diagnosis and therapy; 2) nutrition support pharmacy (recognized since 1988)—specialists promote the maintenance or restoration of optimal nutritional status, designing and modifying treatment according the needs of the patient; 3) oncology pharmacy (recognized since 1996)—specialists address the pharmaceutical care of patients with cancer; 4) pharmacotherapy (recognized since 1988)—specialists are responsible for ensuring the safe, appropriate, and economic use of drugs in patient care and frequently serve as a primary source of drug information for other health care professionals; and 5) psychiatric pharmacy (recognized since 1992)—specialists address the pharmaceutical care of patients with psychiatric disorders.

Position 1

The American College of Physicians–American Society of Internal Medicine (ACP–ASIM) supports research into the effects of pharmacy automation and the move to the PharmD degree on pharmacy practice.

Two thirds of pharmacists work in community pharmacies (6). However, it is likely that pharmacists will further branch out into areas such as research, consulting, and hospital work because automation in pharmacy is growing, pharmacy technician responsibilities are increasing, and the PharmD will be the sole pharmacy degree offered in the 21st century.

Pharmacists will be seeking new roles, especially because store-based pharmacists in July through August 1999 spent more than 60% of their time processing and dispensing orders, according to a 1999 survey (7). Clearly, much of this time will be freed up as automated dispensing and use of pharmacy technicians increase. Long-term research is needed to evaluate the effects of automated dispensing and the move to the PharmD on the pharmacy profession. These events will affect not only pharmacy practice but physician practice as well.

PHARMACEUTICAL CARE

Pharmacists are moving from prescription provider to pharmaceutical care provider. The American Pharmaceutical Association defines pharmaceutical care as patient-centered, outcomes-oriented, pharmacy practice. Pharmaceutical care is designed to promote health; prevent disease; and assess, monitor, initiate, and modify medication use to assure that drug therapy regimens are safe and effective (8). As part of the pharmaceutical care plan, pharmacists help assess therapeutic needs, prevent adverse drug reactions, develop patient-specific therapy, manage chronic disease, and monitor follow-up care (8).

COLLABORATIVE CARE AND THE VALUE OF PHARMACIST INVOLVEMENT

Collaborative drug therapy is one of the best examples of how pharmacists work with physicians. It is designed to maximize the patient's health-related quality of life, reduce the frequency of avoidable drug-related problems, and improve the societal benefits of pharmaceuticals (9). This process involves the pharmacist, physician, other health care professionals, and the patient. It includes basic dispensing functions, drug information services, the solving of patient-related and medication-related problems, and decision making regarding drug prescribing and monitoring and drug regimen adjustments. However, to participate in collaborative drug therapy, pharmacists need access to patients, access to medical records, knowledge and skills, and documentation and compensation for their activities (9).

Collaborative drug therapy covers a wide array of pharmacist activities and takes place in various settings. Several studies have assessed pharmacist participation in drug therapy in different settings, including pharmacy-based disease management and pharmacists on hospital rounds. Generally, pharmacist involvement in drug therapy has been successful, leading to improved patient care and safety and lowered medical costs.

Numerous studies have evaluated the value of the pharmacist in patient care, and they overwhelmingly describe successful ventures, although predominantly in hospital settings. Four clinical pharmacy services were associated with lower mortality rates in hospitals: clinical research, drug information services, medication admission histories, and participation on a cardiopulmonary resuscitation team (10). In addition, six clinical pharmacy services were associated with significantly lower total health care costs: drug use evaluation, drug information services, adverse drug report monitoring, drug protocol management, medical rounds participation, and medication admissions histories (10).

Pharmacist-initiated interventions at a large university hospital significantly decreased drug costs. A study group randomly assigned to receive pharmacist intervention had 41% lower drug costs than those of the control group. Anti-infective agents had the greatest cost savings (11). The interventions had no effect on length of hospital stay, in-hospital mortality, 30-day readmissions, or the need to readminister the targeted medication or to restart intravenous therapy, but the interventions did provide an equivalent level of care (11). Although the results of this study and others were positive, it is not clear whether pharmacist participation is more effective than more modern interventions that have been shown to improve drug use—namely, computer-generated reminders to physicians at the point of care.

Similarly, pharmacist participation on physician rounds in the intensive care unit has been found useful in preventing medication errors (12). Pharmacists reviewed medication orders at the time of prescribing and made suggestions as necessary. The rate of preventable adverse drug events was reduced by 66%, and physicians accepted 362 of the 365 pharmacist recommendations (12).

In addition to studies of clinical pharmacy services offered in the hospital setting, researchers have also analyzed the effects of pharmacist participation in local clinics and pharmacies, primarily in disease management and immunization. Disease state management credentialing is available for pharmacists through the National Association of Boards of Pharmacy and the National Institute for Standards in Pharmacist Credentialing. Pharmacists may take one of four examinations that are designed to measure knowledge and judgment in providing disease state management services. Examinations are available for anticoagulation, asthma, diabetes mellitus, and dyslipidemia (13).

Pharmacists have been involved in demonstration projects on lipid disorders, anticoagulation clinics, diabetes, asthma, and vaccination (10). These studies indicate that patient outcomes improved and medical costs decreased as a result of pharmacist involvement. By including clinical pharmacists on a heart failure management team, one cardiology clinic significantly reduced all-cause mortality and heart failure events (14).

In addition to heart failure management programs, pharmacists have also been involved in diabetes-monitoring programs. In one study, pharmacists developed a community pharmacy–based diabetes monitoring program. Data on diabetes care were gathered at prescription refills. The average morning blood glucose values decreased, and a medication adherence rate of 90% was maintained over a 1-year period (15). In addition, pharmacists recommended drug therapies to physicians, and physicians accepted 75% of these recommendations (15).

Position 2

To improve patient safety and reduce medical errors, ACP–ASIM supports physician-directed pharmacist–physician collaborative practice agreements limited to pharmacist involvement in patient education and hospital rounds.

1. *Expanded roles for pharmacists should not be solely based on cost savings.*
2. *The responsible physician and pharmacist should be compensated for their time spent on collaborative services.*
3. *The physician should solely determine if a relationship will be formed with a pharmacist.*
4. *The physician should solely and individually refer a patient to a pharmacist.*
5. *Only the physician shall and must diagnose the patient's condition prior to any referral (16).*

Physicians are qualified to diagnose and treat patients, while pharmacist expertise lies with pharmaceuticals. An improved, more collaborative relationship between the two disciplines could improve patient care and safety and reduce medical costs. However, it is imperative that reduced cost is not the only factor considered in pharmacist scope of practice. In addition, we need to ensure that physicians control prescriptive rights and have the final approval over all patient care decisions. Decisions about the most appropriate drug for a patient's condition are often subtle and require a level of experience and training that is not provided in obtaining a PharmD degree. This, in fact, is why physician training entails many years of practical supervised experience. This is not to say that PharmD training does not add benefit in a collaborative relationship, but rather that the benefit is incremental and not a substitute for that of the physician, whose role is primary.

Pharmacist involvement in patient care activities may improve patient outcomes, but it will also consume physicians' time. For physicians working in a hospital setting, medication advice can be obtained with relatively few diversions from other responsibilities because an in-hospital physician's involvement with pharmacists is largely restricted to the physician's limited time on service and the number of patients on rounds. However, for physicians in community-based practices, working with pharmacists may present more serious time-management problems. Physicians will have to make decisions based on how much time, realistically, their offices are able to spend working with pharmacists.

Physicians are compensated for time spent working with physician extenders, for example, nurse practitioners and physician assistants. A similar payment system should be established for physicians' collaborative work with pharmacists. Funds should not simply be shifted from one provider to the other; instead, new sources of revenue will need to be identified.

Pharmacists continue to successfully expand their scope of practice. With the transition to the PharmD degree and automated drug dispensing, pharmacists are being trained to take on a greater patient care role. Instead of taking an adversarial position, the medical community must work together with the pharmacy profession to enhance patient care and safety while maintaining physician responsibility for continuous patient care. By combining the efforts of organized medicine and pharmacy, medication errors can be reduced and patients may live fuller, healthier lives.

Simultaneously, the pharmacy and medical professions should use their collective influence to promulgate better education of physicians in the use of drugs. Doing so will reduce medication errors and result in better patient care. Examples of efforts that might occur in this area are working with the U.S. Pharmacopeia and the Food and Drug Administration to promote better reporting mechanisms for drug errors or supporting Centers for Education and Research in Therapeutics.

Position 3

ACP–ASIM opposes independent pharmacist prescriptive privileges and initiation of drug therapy.

Although several studies describe the benefits of pharmacist and physician collaboration, little evidence supports pharmacist prescribing or initiation of drug therapy (10). Physicians have complete medical histories of patients, including awareness of other conditions and past treatments. Without that information, the appropriate training, and the reassurance of patient safety, ACP–ASIM cannot support independent prescriptive authority or drug therapy initiation for pharmacists.

Physician training is rigorous and heavily relies on patient interaction. It entails numerous years of practical, supervised "hands-on" training because of the subtleties of diagnosis and therapeutics that are the reality of patient care. The insight that this experience provides cannot be replicated in a less time-intensive and rigorous experience. This is not to criticize pharmacist education but instead to emphasize that the goals of the two educational paths are different, as are the outcomes in terms of skill set. Pharmacists do not have the exposure and experience to diagnose and prescribe medications for patients. This is clearly an area that should remain under physician authority.

Position 4

ACP–ASIM supports the use of the pharmacist as immunization information source, host of immunization sites, and immunizer, as appropriate and allowed by state law. ACP–ASIM will work with pharmacy organizations to increase immunization awareness.

Thirty states already allow pharmacists to administer immunizations (17). Because of the extensive state legislation that already exists, allowing pharmacists and nurses to administer immunizations, the potential benefit of nonphysician immunization of patients is widely recognized. Pharmacists provide increased access to immunization through extended business hours and locations. Increased access to immunization by trained pharmacy professionals will help to decrease antibiotic resistance and increase adult immunization. Pharmacists and physicians should focus on delivering vaccines to those populations most at risk, in an attempt to decrease mortality rates from preventable diseases.

Position 5

ACP–ASIM reiterates its support of its 1990 therapeutic substitution position. ACP–ASIM resolves to work with pharmacists in designing therapeutic substitution policies that ensure the highest level of patient care and safety.

Another important issue in physician–pharmacist collaboration is therapeutic substitution—the selection of a chemically different drug that is considered to be a therapeutic alternative with a comparable therapeutic effect. The current ACP–ASIM policy of therapeutic substitution states the following (18):

> Position 1. Therapeutic substitution is appropriate only in hospitals with an effectively functioning formulary system and Pharmacy and Therapeutics Committee.

> Position 2. Therapeutic substitution jeopardizes patient management when immediate prior consent is not obtained from the authorized prescriber and when documentation of substitutions is untimely or improper. Such practices must not be permitted.
>
> Position 3. The practice of therapeutic substitution may be acceptable in ambulatory settings that meet standards comparable to those of institutional settings.
>
> Position 4. Effective therapeutics require physicians to be well educated in therapeutics and to instruct patients about the proper use and effects of prescribed medication.

The American College of Clinical Pharmacy also supports therapeutic substitution when physicians and pharmacists work together to develop effective policies that maximize patient care at the best price. The American College of Clinical Pharmacy's therapeutic interchange guidelines are as follows (19):

> Guideline 1. Therapeutic interchange is appropriate in institutional and ambulatory settings that have a functioning formulary system and Pharmacy and Therapeutics Committee or equivalent advisory committee.
>
> Guideline 2. A continuous drug use evaluation process must be in place for regular review of endorsed therapeutic interchange policies and procedures.
>
> Guideline 3. Therapeutic interchange, as defined herein, may be executed by pharmacists if the authorized prescriber is notified either verbally or in writing within a reasonable time frame, and if the pharmacists have access to medical records and appropriate laboratory or other test results as required by the therapeutic interchange policy. Exceptions to this procedure must be stated clearly in the policy.
>
> Guideline 4. The Pharmacy and Therapeutics Committee or its equivalent should ensure that professional staff are educated regarding the rationale, policies, and procedures for therapeutic interchange.
>
> Guideline 5. The therapeutic interchange policies should define a mechanism that enables authorized prescribers to disallow therapeutic interchange.

Ensuring safe, effective therapeutic substitution is a high priority for both pharmacists and physicians. Immediate prior consent by a physician is essential in maintaining patient management responsibilities and ensuring patient safety. The physician, as patient care manager, and pharmacist, as medication expert, are in a unique position to work together for improved therapeutic substitution policies that provide high-quality care and cost savings.

REIMBURSEMENT AND LIABILITY

Reimbursement for pharmacists' professional services, other than dispensing, is currently receiving attention by the states. Several states have requested a waiver 11 from Medicaid to develop demonstration projects with pharmacists (20). Mississippi received the first Medicaid waiver (effective April 1998) from the Centers for Medicare and Medicaid Services to reimburse pharmacists for disease management of patients. Reimbursement is available for asthma, diabetes, hyperlipidemia, and anticoagulation services (21). The Mississippi project was an effort to evaluate whether pharmacists are better suited than physicians to cost-effectively spend time educating and monitoring patients.

New Mexico also has a demonstration project that allows pharmacists prescriptive authority according to protocol; however, unlike in Mississippi, pharmacists are not restricted to managing specific diseases (20). Only board-certified pharmacists are allowed to participate, and they must be supervised by a physician approved by the New Mexico Board of Medical Examiners. Pharmacists and physicians meet every 2 weeks, and reimbursement is arranged by physicians.

However, as pharmacists begin to receive reimbursement for their patient care services, they also become increasingly liable for their actions. In January 2000, the Alabama Supreme Court held that pharmacies and pharmacists are "health care providers," thereby governed by the Alabama Medical Liability Act. In August 2000, the Texas Court of Appeals ruled that pharmacists do not have a general duty to warn about all possible side effects or adverse effects but acknowledged that they do have a duty to warn when they are aware of information that would raise the importance or probability of such effects (22). Because reimbursement was not related to the Court's decision, however, payment and liability issues were separated.

Currently, pharmacists are not approved providers under Medicare except to perform immunizations (20). For pharmacists to be added to the list of providers, the Social Security Act would need to be amended. The Centers for Medicare and Medicaid Services implemented a regulation that provides Medicare coverage for training programs to help beneficiaries with diabetes mellitus to control their disease. Medicare pays certified diabetes educators and dietitians to provide training to help control the disease and avoid complications, such as blindness, amputation, or kidney disease. To be certified, trainers must be employees of a program certified by the Centers for Medicare and Medicaid Services and part of a collaborative team providing services to beneficiaries. Some pharmacists qualify as certified providers if they are a Medicare supplier of durable medical equipment and if they meet quality standards (23).

The Medicare proposal would help newly diagnosed diabetic patients, those who have not received training, or those in serious danger of complications from diabetes mellitus. A physician must certify that a patient needs the service under a comprehensive plan of care. With the approval of their physician or qualified practitioner, eligible beneficiaries would initially receive up to 10 hours of group training and an annual 1-hour refresher course (23).

CONCLUSION

Clearly, pharmacist scope of practice is expanding, and the medical community must proactively respond to the pharmacy movement. The ACP–ASIM remains committed to exploring new roles for nonphysicians and helping to ensure that the practice of medicine remains with physicians. By partnering collaboratively with pharmacists, physicians will be able to avoid "turf" battles and focus on their primary mission—high-quality patient care. Pharmacists can educate physicians on drug interactions and cost savings and educate patients on drug safety, while physicians provide safe, effective care to patients.

However, there are striking differences in physician work settings—that is, hospital versus private practice. Policies must be adapted to meet individual office needs. The ACP–ASIM is committed to fostering effective and productive collaborative relationships between physicians and pharmacists, while securing the physicians' role as the medical expert who is responsible for the diagnosis and treatment of patients. There is no substitute for medical school training. The ACP–ASIM looks forward to further research on the effect on the pharmacy profession by drug dispensing automation and the move to the PharmD degree. In addition, research evaluating the effects of pharmacist and physician collaboration on physicians' time with patients and studies examining the outcomes of a community-based PharmD system is needed.

APPENDIX: SUMMARY OF RECENT STATE LEGISLATION

Collaborative Practice Agreements

Data in this appendix were obtained from reference 24.

A survey by the National Association Boards of Pharmacy showed that Idaho, Louisiana, Nebraska, Ohio, and Tennessee joined a growing number of jurisdictions permitting pharmacists to develop collaborative practice agreements with prescribers. Such agreements generally allow pharmacists to initiate or modify patient medication regimens pursuant to approved protocol. States also explored this issue in 1999, when 11 states enacted legislation allowing collaborative practice agreements with other health care providers (Arkansas, California, Georgia, Minnesota, Nevada, North Carolina, Oregon, Texas, Utah, Virginia, and Wyoming).

A Minnesota law expanded pharmacists's scope of practice to include drug administration for first dosages and emergencies and participation in drug-therapy monitoring, selecting therapeutic devices, and drug or drug-related research. This law also permits participation in managing and modifying drug therapy on a case-by-case basis according to a written protocol between the specific pharmacist and an individual practitioner who has prescribing authority and who is responsible for the patient's care. Virginia authorized pharmacists to enter into collaborative agreements with physicians, osteopathic physicians, or podiatrists. Another law defined "collaborative agreement" and held that such an agreement is not required for the management of patients in an in-patient facility.

Scope of Practice

2000 was an active year for legislation regarding pharmacist scope of practice. Vermont enacted legislation making licensure changes. Arizona enacted a bill changing licensure, fees, and prescription labeling. Georgia now provides qualifications for pharmacists authorized to modify drug therapy. Maryland required pharmacists to maintain a log of new and refill prescriptions. Kansas allowed pharmacists to administer vaccinations to persons 18 years of age or older. Legislation in six states (Alabama, California, Colorado, Delaware, New Hampshire, and Virginia) has passed in at least one chamber. New Hampshire's bill would allow pharmacists to sell syringes without a prescription, and Virginia's bill addresses radiopharmaceuticals, prescribers, and distribution.

In 1999, bills relating to scope of practice became law in 17 states (Arkansas, California, Georgia, Louisiana, Maine, Maryland, Minnesota, Missouri, Nebraska, North Dakota, Nevada, Oregon, Tennessee, Texas, Utah, Virginia, and Wyoming).

Areas of expansion of the pharmacist scope of practice included authorization to administer medications and injections, perform physical assessments, and order laboratory tests. Arkansas, California, Georgia, Minnesota, Oregon, Texas, and Utah enacted some provision allowing pharmacists to perform what otherwise have been "hands-on" practitioner activities. Wyoming authorized disease management by adding collaborative pharmaceutical care to the definition of practicing pharmacy. Arkansas codified disease management in its state pharmacy act.

Legislation enacted in Virginia created provisions focusing on the duty of a pharmacist in charge of an automated drug-dispensing system for a hospital. A law in Utah expanded the definition for the practice of pharmacy to include administering and distributing prescription drugs and devices pursuant to appropriate protocols. A law in North Dakota allowed registered pharmacy technicians to receive orally transmitted new or refill prescriptions. A law in Georgia amended several provisions related to pharmacists, including the scope of practice and licensure requirements for nuclear pharmacists.

Maine amended many provisions related to pharmacists and established a statutory review committee to review the scope of practice for pharmacists and, if necessary, to make recommendations for change. The review must address the issues of drug administration and collaborative practice and the current regulatory relationship between the Board of Pharmacy and institutional pharmacies. Effective 6 January 1999, the Alabama Board of Pharmacy adopted regulations that allow pharmacists to provide pharmaceutical care to patients by administering immunizations to eligible patients with valid prescription orders.

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LETTERS

The Editors welcome submissions for possible publication in the Letters section. Authors of letters should: • Include no more than 300 words of text, three authors, and five references • Type with double-spacing • Send a diskette, three copies of the letter, an authors' form (see Table of Contents for location) signed by all authors, and a cover letter describing any conflicts of interest related to the contents of the letter. *Annals* welcomes electronically submitted letters: www.acponline.org/shell-cgi/letter-article.pl.

Osteoarthritis: New Insights

TO THE EDITOR: The authors of the Systemic and Topical Treatments section in part 2 of the National Institutes of Health conference on osteoarthritis (1) did not provide a fair assessment of glucosamine and chondroitin compared with their assessment of the cyclooxygenase (COX)-2 inhibitors. Seeing that one of the three authors is sponsored by the manufacturer of the COX-2 inhibitor rofecoxib, one cannot help but suspect that market-share competition may have had something to do with the bias.

The authors state, "Of note, most (if not all) trials [of glucosamine and chondroitin] were sponsored by a manufacturer of the product." And the COX-2 inhibitor trials weren't? The authors state that independent studies are needed to test glucosamine and chondroitin. If so, then why isn't the same true for celecoxib and rofecoxib? Consistent with the overall disparaging tone of their discussion of glucosamine and chondroitin, the authors also state that trials of glucosamine and chondroitin measured symptoms only and that therefore no inferences can be drawn about their effect on the pathologic progression of osteoarthritis. True, but why didn't they make that observation about COX-2 inhibitors, which also have not been shown to affect disease progression? In addition, the authors mentioned nothing about the excellent safety profile of glucosamine and chondroitin, which gives these drugs a significant advantage over nonsteroidal anti-inflammatory drugs and COX-2 inhibitors.

Attaching a financial disclosure to the end of a presumably scientific and impartial article does not relieve authors of their responsibility to be impartial. These authors were not only partial but also had the cheek to impugn studies for their sponsorship when one of them was likewise sponsored.

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TO THE EDITOR: The authors of the review series on osteoarthritis (1) are to be commended for their effort to focus attention on advances in treatment and for their well-referenced, concise summary. Primary care providers need to become familiar with all options in order to offer comprehensive treatment programs. The omission of viscosupplementation, therefore, was surprising. The U.S. Food and Drug Administration approved hyaluronan-based viscosupplements in 1997 for the treatment of symptoms of knee osteoarthritis after failure of nonpharmacologic therapy and acetaminophen. Viscosupplements have been used clinically for osteoarthritis in Europe and Japan for over 10 years, and a high-molecular-weight preparation, hylan G-F 20, has been used in Europe and Canada for over 5 years. Blinded, multicenter clinical trials have demonstrated efficacy for hylan versus intraarticular saline or oral NSAIDs in knee osteoarthritis, grades 1 through 3 (2, 3).

In my knee-only orthopedic practice, since October 1997, 1500 knees with predominately severe osteoarthritis (>80%, grade 4) have been treated with hylan. Symptomatic relief, assessed on a visual analogue scale, has been dramatic and sustained for months or years in many of these patients, in whom nonsteroidal inflammatory drugs, corticosteroids, and sometimes arthroscopic surgery had failed (4). The side effects of viscosupplementation are usually minor (5) and may be associated with inaccurate, extraarticular placement of the viscosupplement. We confirm intraarticular placement of the needle tip with fluoroscopy and have had a very low rate of side effects.

Physicians who treat osteoarthritis cannot rely on a single method but must select among options, according to such factors as radiographic and symptomatic severity, inflammatory features, patient age and lifestyle, response to previous treatments, and comorbid conditions. Until medical science develops a cure, viscosupplementation merits recognition as a valuable tool for relief of osteoarthritic knee pain.

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TO THE EDITOR: It is surprising that among the 135 citations in the otherwise comprehensive review of osteoarthritis treatment by a panel of U.S. and foreign authorities, none referred to pulsed elec-

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tromagnetic field therapy (1). There is no dearth of articles on various aspects of this therapy in peer-reviewed publications, including two articles in a Canadian journal reporting on double-blind studies conducted at a hospital affiliated with Yale Medical School (2, 3). Several presentations on pulsed electromagnetic fields for osteoarthritis were made at the 10th and 11th International Congress on Stress and the annual meeting of the Biolelectromagnetics Society. Of these presentations, one reported on results of double-blind and open-label clinical trials in over 100 000 patients (4). In 2000, more than 100 000 patients received pulsed-signal therapy at more than 400 hospitals and medical clinics in 17 countries, where it is reimbursed by fiscal intermediaries and government agencies because of its proven record of cost-effectiveness and safety.

The nine noninvasive, 1-hour daily treatments have no adverse side effects. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and instruments validated by the Outcome Measures in Arthritis Clinical Trials III reveal complete or very significant pain relief in most patients. Modified Ritchie scales and the WOMAC Index, as well as global evaluations of improvement by patients and physicians, also confirm increased mobility and range of motion that persist on long-term follow-up.

Pulsed-signal therapy is designed to reproduce the piezoelectric signal responsible for stimulating chondrocyte activity when bone is subjected to pressure. Support for its clinical efficacy comes from studies of in vitro cell culture showing that pulsed-signal therapy stimulates proteoglycan synthesis and chondrocyte formation (5). Pulsed electromagnetic field therapy has long been approved for treating bone fractures that have failed to unite and has been successful in hundreds of thousands of patients, including some in whom nonunion had persisted for 15 or more years. It may also be the safest and most effective treatment for osteoarthritis.

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TO THE EDITOR: A recommendation for osteoarthritis treatment (1) states, "The choice between a nonselective NSAID [nonsteroidal anti-inflammatory drug] and a COX-2–specific inhibitor should be made after evaluation of risk factors, particularly for upper gastrointestinal and renal toxicity." This assumes that 1) all "NSAIDs" are similar, 2) all "COX-2s" are similar, and 3) the difference (COX-1 sparing) accounts for less toxicity. Specificity for cyclooxygenases does not determine the side effect profile of NSAIDs. Differences among COX-2s (for example, in effects on renal function) may be as great as differences from certain nonselective NSAIDs (2); the same may be true for cardiovascular events (3). NSAIDs differ in gastrointestinal toxicity, and COX-2s have been shown to be superior to only a few NSAIDs. For example, no study has found COX-2s to result in fewer endoscopic or clinical ulcers, or ulcer complications, than the nonselective NSAID nabumetone; in the only comparative study, no ulcers occurred with either nabumetone or rofecoxib (4). A review of studies with nabumetone found no evidence that nabumetone is more likely to cause ulcers than COX-2s (5). Given variable safety profiles within both types of NSAIDs, we should not focus on COX-1 sparing and assume that this explains differences. If it did, completely inhibiting COX-1 by coadministering low-dose aspirin should completely abolish any difference between COX-2s and NSAIDs. While that may be true for ulcer complications (as shown in the Celecoxib Long-Term Arthritis Safety Study), which depend heavily on platelet inhibitors, it has not been proven yet for ulcerations. Factors other than COX specificity may be as or more important in ulcer formation: In contrast to NSAIDs (which have higher rates of gastrointestinal toxicity), all COX-2s and nabumetone are nonacidic and lack local effects on the mucosa. Evidence-based medicine requires that we base conclusions on data, not presumed mechanisms. Celecoxib and rofecoxib have shown gastrointestinal advantages over diclofenac, naproxen, and high-dose ibuprofen (2400 mg/d), but not over such NSAIDs as nabumetone, etodolac, and meloxicam.

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IN RESPONSE: As coauthors of the review of therapy in osteoarthritis who are not funded by companies producing COX-2 inhibitors or any brands of glucosamine or chondroitin, we can comment impartially on Dr. Lindow's concerns about any bias in advocating COX-2 inhibitors compared with glucosamine or chondroitin. We consider glucosamine and chondroitin promising agents for osteoarthritis. Our meta-analysis of trials of these agents suggested several biases, including probable publication bias, that should inject caution into interpretation of the positive trial results. We should note that since the publication of our meta-analysis, several new randomized, placebo-controlled trials have been published that have not shown efficacy of either glucosamine or chondroitin (1–3). An additional null trial was presented at the 2000 American College of Rheumatology meeting. We know of no published or unpublished data suggesting that COX-2 inhibitors have no significant effect relative to placebo in patients with osteoarthritis. Furthermore, COX-2 inhibitors underwent critical scrutiny by the U.S. Food and Drug Administration before approval; glucosamine and chondroitin have not been so evaluated. Thus, we believe that there is stronger evidence for relief of symptoms in osteoarthritis with COX-2 inhibitors than with glucosamine and chondroitin, for which the data are genuinely conflicting. It is to be hoped that the large National Institutes of Health–funded trial of glucosamine and chondroitin will help definitively resolve the issue of their place in osteoarthritis management. We concur with Dr. Lindow that these agents are safe and did not mean to imply that COX-2, glucosamine, or chondroitin clearly affects structural disease progression. However, such an effect for glucosamine has recently been suggested by a large-scale, long-term randomized trial.

Dr. Waddell advocates viscosupplementation in the form of hyaluronic injections for the treatment of osteoarthritis. This treatment is controversial, and the largest trial's intention-to-treat analysis has shown no evidence of efficacy compared with placebo saline injections in the knee (4) (**Table**). In this large multicenter trial, no difference was seen between placebo and hyaluronic acid. Other multicenter trials of hyaluronic acid have been similarly null (5).

Dr. Rosch advocates pulsed electromagnetic fields for osteoarthritis, a treatment that he contends has been shown to be efficacious. Two reasonably well-done although small-scale clinical trials suggest that pulse electromagnetic fields may relieve symptoms in patients with osteoarthritis. A small trial (6) of 27 patients reported improvement in those treated with pulsed-signal therapy, although the improvement in the active versus placebo groups was not compared statistically and the placebo group also experienced modest improvement. In a larger trial reported by some of the same investigators (7), the improvement experienced by treated patients versus placebo recipients reached significance for some measures of outcome at some time points but not others. Multiple outcomes were evaluated at several time points. Results of both trials suggested that pulsed-signal therapy had a modestly greater effect than placebo. Thus, we would characterize pulsed-signal therapy as an experimental therapy whose efficacy must be demonstrated by additional data.

Table. **Effect of Hyalgan Compared with Placebo on Pain during a 50-Foot Walk: Intention-to-Treat Analysis***

Treatment Group	Mean Baseline Value	Mean Value at 12 Weeks	Mean Value at 26 Weeks
	←——	*mm*	——→
Hyalgan	54	23	27
Placebo	55	24	28

*Based on data from reference 4. Pain was measured on a 10-cm visual analogue scale. $P > 0.2$ for the difference between groups.

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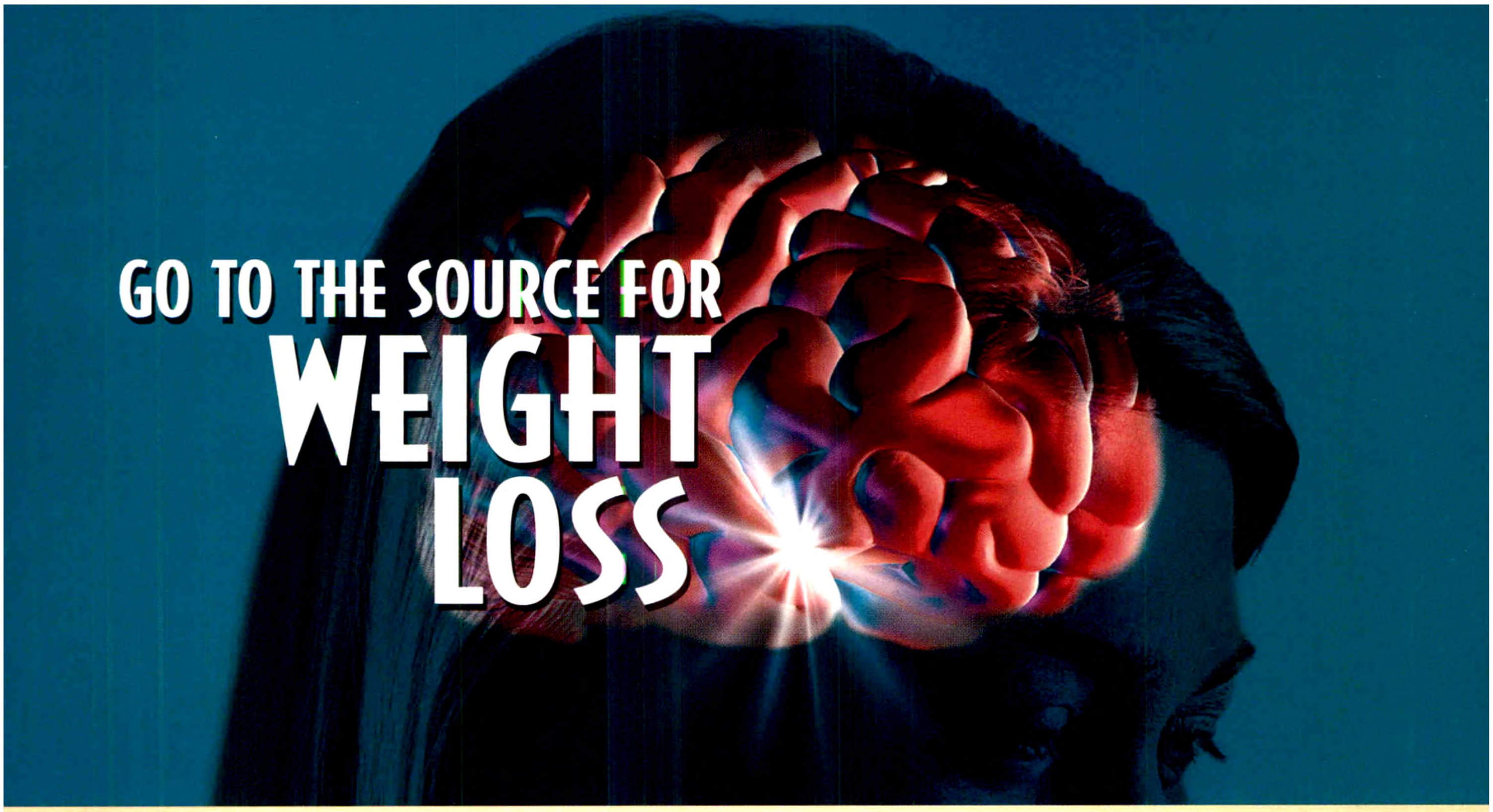
GO TO THE SOURCE FOR
WEIGHT
LOSS

MERIDIA HELPS DELIVER SIGNIFICANT WEIGHT LOSS AND 2-YEAR MAINTENANCE[1]

- MERIDIA reduces food intake by reuptake inhibition of primarily norepinephrine and serotonin—with no release of monoamines[2]
- In 11 double-blind, placebo-controlled studies from 12 to 52 weeks in duration, weight was significantly reduced with sibutramine vs placebo[2]
- In a 2-year study, 43% of patients on MERIDIA plus diet and exercise (n=204) maintained at least 80% of the weight loss achieved at 6 months vs 16% on diet and exercise alone (n=57); *P*<.001[1]

Mean weight loss:
26 LB AT 6 MONTHS
in 2-year study[1]

INDICATIONS AND SAFETY INFORMATION

MERIDIA is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced-calorie diet.[2]

MERIDIA is recommended for obese patients with an initial BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).[2]

MERIDIA is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs), who have anorexia nervosa, who have hypersensitivity to sibutramine or any of the inactive ingredients of MERIDIA, and those taking other centrally acting appetite-suppressant drugs.[2]

MERIDIA substantially increases blood pressure in some patients. Regular monitoring of blood pressure is required when prescribing MERIDIA.[2]

Most common adverse events with MERIDIA include headache (30%), dry mouth (17%), anorexia (13%), constipation (12%), and insomnia (11%).[2]

MERIDIA® CIV
(sibutramine hydrochloride monohydrate) Capsules

BECAUSE THE WEIGHT CAN'T WAIT

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Please see brief summary of prescribing information on the following page.

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BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

MERIDIA® C IV

(sibutramine hydrochloride monohydrate) Capsules

CONTRAINDICATIONS: MERIDIA is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs) (see "WARNINGS").

MERIDIA is contraindicated in patients with hypersensitivity to sibutramine or any of the inactive ingredients of MERIDIA.

MERIDIA is contraindicated in patients who have anorexia nervosa.

MERIDIA is contraindicated in patients taking other centrally acting appetite suppressant drugs.

WARNINGS: Blood Pressure and Pulse: MERIDIA SUBSTANTIALLY INCREASES BLOOD PRESSURE IN SOME PATIENTS. REGULAR MONITORING OF BLOOD PRESSURE IS REQUIRED WHEN PRESCRIBING MERIDIA.

In placebo-controlled obesity studies, MERIDIA 5 to 20 mg once daily was associated with mean increases in systolic and diastolic blood pressure of approximately 1 to 3 mm Hg relative to placebo, and with mean increases in pulse rate relative to placebo of approximately 4 to 5 beats per minute. Larger increases were seen in some patients, particularly when therapy with MERIDIA was initiated at the higher doses (see table below). In pre-marketing placebo-controlled obesity studies, 0.4% of patients treated with MERIDIA were discontinued for hypertension (SBP ≥160 mm Hg or DBP ≥95 mm Hg), compared with 0.4% in the placebo group, and 0.4% of patients treated with MERIDIA were discontinued for tachycardia (pulse rate ≥100 bpm), compared with 0.1% in the placebo group. Blood pressure and pulse should be measured prior to starting therapy with MERIDIA and should be monitored at regular intervals thereafter. For patients who experience a sustained increase in blood pressure or pulse rate while receiving MERIDIA, either dose reduction or discontinuation should be considered. MERIDIA should be given with caution to those patients with a history of hypertension, and should not be given to patients with uncontrolled or poorly controlled hypertension.

Percent Outliers in Studies 1 and 2

	% Outliers*		
Dose (mg)	SBP	DBP	Pulse
Placebo	9	7	12
5	6	20	16
10	12	15	28
15	13	17	24
20	14	22	37

* Outlier defined as increase from baseline of ≥15 mm Hg for three consecutive visits (SBP), ≥10 mm Hg for three consecutive visits (DBP), or pulse ≥10 bpm for three consecutive visits.

Potential Interaction With Monoamine Oxidase Inhibitors: MERIDIA is a norepinephrine, serotonin and dopamine reuptake inhibitor and should not be used concomitantly with MAOIs (see "PRECAUTIONS", Drug Interactions subsection). There should be at least a 2-week interval after stopping MAOIs before commencing treatment with MERIDIA. Similarly, there should be at least a 2-week interval after stopping MERIDIA before starting treatment with MAOIs.

Concomitant Cardiovascular Disease: Treatment with MERIDIA has been associated with increases in heart rate and/or blood pressure. Therefore, MERIDIA should not be used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.

Glaucoma: Because MERIDIA can cause mydriasis, it should be used with caution in patients with narrow angle glaucoma.

Miscellaneous: Organic causes of obesity (e.g., untreated hypothyroidism) should be excluded before prescribing MERIDIA.

PRECAUTIONS: Pulmonary Hypertension: Certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals have been associated with pulmonary hypertension (PPH), a rare but lethal disease. In pre-marketing clinical studies, no cases of PPH have been reported with MERIDIA® (sibutramine hydrochloride monohydrate) Capsules. Because of the low incidence of this disease in the underlying population, however, it is not known whether or not MERIDIA may cause this disease.

Seizures: During premarketing testing, seizures were reported in <0.1% of MERIDIA treated patients. MERIDIA should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Gallstones: Weight loss can precipitate or exacerbate gallstone formation.

Renal/Hepatic Dysfunction: Patients with severe renal impairment or severe hepatic dysfunction have not been systematically studied; MERIDIA should therefore not be used in such patients.

Interference With Cognitive and Motor Performance: Although sibutramine did not affect psychomotor or cognitive performance in healthy volunteers, any CNS active drug has the potential to impair judgment, thinking or motor skills.

Information For Patients: Physicians should instruct their patients to read the patient package insert before starting therapy with MERIDIA and to reread it each time the prescription is renewed.

Physicians should also discuss with their patients any part of the package insert that is relevant to them. In particular, the importance of keeping appointments for follow-up visits should be emphasized.

Patients should be advised to notify their physician if they develop a rash, hives, or other allergic reactions.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, especially weight-reducing agents, decongestants, antidepressants, cough suppressants, lithium, dihydroergotamine, sumatriptan (Imitrex®), or tryptophan, since there is a potential for interactions.

Patients should be reminded of the importance of having their blood pressure and pulse monitored at regular intervals.

Drug Interactions: ***CNS Active Drugs:*** The use of MERIDIA in combination with other CNS-active drugs, particularly serotonergic agents, has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of MERIDIA with other centrally-acting drugs is indicated (see "CONTRAINDICATIONS" and "WARNINGS").

In patients receiving monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine, selegiline) in combination with serotonergic agents (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine), there have been reports of serious, sometimes fatal, reactions ("serotonin syndrome;" see below). Because MERIDIA inhibits serotonin reuptake, MERIDIA should not be used concomitantly with a MAOI (see "CONTRAINDICATIONS"). At least 2 weeks should elapse between discontinuation of a MAOI and initiation of treatment with MERIDIA. Similarly, at least 2 weeks should elapse between discontinuation of MERIDIA and initiation of treatment with a MAOI.

The rare, but serious, constellation of symptoms termed "serotonin syndrome" has also been reported with the concomitant use of selective serotonin reuptake inhibitors and agents for migraine therapy, such as Imitrex® (sumatriptan succinate) and dihydroergotamine, certain opioids, such as dextromethorphan, meperidine, pentazocine and fentanyl, lithium, or tryptophan. Serotonin syndrome has also been reported with the concomitant use of two serotonin reuptake inhibitors. The syndrome requires immediate medical attention and may include one or more of the following symptoms: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiballismus, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilation, diaphoresis, emesis, and tachycardia.

Because MERIDIA inhibits serotonin reuptake, in general, it should not be administered with other serotonergic agents such as those listed above. However, if such a combination is clinically indicated, appropriate observation of the patient is warranted.

Drugs That May Raise Blood Pressure and/or Heart Rate: Concomitant use of MERIDIA and other agents that may raise blood pressure or heart rate have not been evaluated. These include certain decongestants, cough, cold, and allergy medications that contain agents such as ephedrine, or pseudoephedrine. Caution should be used when prescribing MERIDIA to patients who use these medications.

Drugs That Inhibit Cytochrome P450(3A$_4$) Metabolism: In vitro studies indicated that the cytochrome P450(3A$_4$)-mediated metabolism of sibutramine was inhibited by ketoconazole and to a lesser extent by erythromycin. Clinical interaction trials were conducted on these substrates. The potential for such interactions is described below.

Ketoconazole: Concomitant administration of 200 mg doses of ketoconazole twice daily and 20 mg sibutramine once daily for 7 days in 12 uncomplicated obese subjects resulted in moderate increases in AUC and C_{max} of 58% and 36% for M_1 and of 20% and 19% for M_2, respectively.

Erythromycin: The steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 were evaluated in 12 uncomplicated obese subjects following concomitant administration of 500 mg of erythromycin three times daily and 20 mg of sibutramine once daily for 7 days. Concomitant erythromycin resulted in small increases in the AUC (less than 14%) for M_1 and M_2. A small reduction in C_{max} for M_1 (11%) and a slight increase in C_{max} for M_2 (10%) were observed.

Cimetidine: Concomitant administration of cimetidine 400 mg twice daily and sibutramine 15 mg once daily for 7 days in 12 volunteers resulted in small increases in combined (M_1 and M_2) plasma C_{max} (3.4%) and AUC (7.3%); these differences are unlikely to be of clinical significance.

Alcohol: In a double-blind, placebo-controlled, crossover study in 19 volunteers, administration of a single dose of ethanol (0.5 mL/kg) together with 20 mg of sibutramine resulted in no psychomotor interactions of clinical significance between alcohol and sibutramine. However, the concomitant use of MERIDIA and excess alcohol is not recommended.

Oral Contraceptives: The suppression of ovulation by oral contraceptives was not inhibited by MERIDIA. In a crossover study, 12 healthy female volunteers on oral steroid contraceptives received placebo in one period and 15 mg sibutramine in another period over the course of 8 weeks. No clinically significant systemic interaction was observed; therefore, no requirement for alternative contraceptive precautions are needed when patients taking oral contraceptives are concurrently prescribed sibutramine.

Drugs Highly Bound to Plasma Proteins: Although sibutramine and its active metabolites M_1 and M_2 are extensively bound to plasma proteins (≥94%), the low therapeutic concentrations and basic characteristics of these compounds make them unlikely to result in clinically significant protein binding interactions with other highly protein bound drugs such as warfarin and phenytoin. *In vitro* protein binding interaction studies have not been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenicity:*** Sibutramine was administered in the diet to mice (1.25, 5 or 20 mg/kg/day) and rats (1, 3, or 9 mg/kg/day) for two years generating combined maximum plasma AUC's of the two major active metabolites equivalent to 0.375 and 15.75 times, respectively, those following a daily human dose of 15 mg. There was no evidence of carcinogenicity in mice or in female rats. In male rats there was a higher incidence of benign tumors of the testicular interstitial cells; such tumors are commonly seen in rats and are hormonally mediated. The relevance of these tumors to humans is not known.

Mutagenicity: Sibutramine was not mutagenic in the Ames test, *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes or micronucleus assay in mice. Its two major active metabolites were found to have equivocal bacterial mutagenic activity in the Ames test. However, both metabolites gave consistently negative results in the *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes, *in vitro* DNA-repair assay in HeLa cells, micronucleus assay in mice and *in vivo* unscheduled DNA-synthesis assay in rat hepatocytes.

Impairment of Fertility: In rats, there were no effects on fertility at doses generating combined plasma AUC's of the two major active metabolites up to 32.25 times those following a human dose of 15 mg. At 13 times the human combined AUC, there was maternal toxicity, and the dams' nest-building behavior was impaired, leading to a higher incidence of perinatal mortality; there was no effect at approximately 4 times the human combined AUC.

Pregnancy: ***Teratogenic Effects - Pregnancy Category C:*** Radiolabeled studies in animals indicated that tissue distribution was unaffected by pregnancy, with relatively low transfer to the fetus. In rats, there was no evidence of teratogenicity at doses of 1, 3, or 10 mg/kg/day generating combined plasma AUC's of the two major active metabolites up to approximately 32.25 times those following human dose of 15 mg. In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUC's greater than approximately 5 times those following the human dose of 15 mg caused maternal toxicity. At markedly toxic doses, Dutch Belted rabbits had a slightly higher than control incidence of pups with a broad short snout, short rounded pinnae, short tail and, in some, shorter thickened long bones in the limbs; at comparably high doses in New Zealand White rabbits, one study showed a slightly higher than control incidence of pups with cardiovascular anomalies while a second study showed a lower incidence than in the control group.

No adequate and well controlled studies with MERIDIA have been conducted in pregnant women. The use of MERIDIA during pregnancy is not recommended. Women of childbearing potential should employ adequate contraception while taking MERIDIA. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing Mothers: It is not known whether sibutramine or its metabolites are excreted in human milk. MERIDIA is not recommended for use in nursing mothers. Patients should be advised to notify their physician if they are breast-feeding.

Pediatric Use: The safety and effectiveness of MERIDIA in pediatric patients under 16 years of age have not been established.

Geriatric Use: Clinical studies of MERIDIA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: In placebo-controlled studies, 9% of patients treated with MERIDIA (n = 2068) and 7% of patients treated with placebo (n = 884) withdrew for adverse events.

In placebo-controlled studies, the most common events were dry mouth, anorexia, insomnia, constipation and headache. Adverse events in these studies occurring in ≥1% of MERIDIA treated patients and more frequently than in the placebo group are shown in the following table.

	Obese Patients in Placebo-Controlled Studies	
BODY SYSTEM	MERIDIA® (n = 2068)	Placebo (n = 884)
Adverse Event	% Incidence	% Incidence
BODY AS A WHOLE:		
Headache	30.3	18.6
Back pain	8.2	5.5
Flu syndrome	8.2	5.8
Injury accident	5.9	4.1
Asthenia	5.9	5.3
Abdominal pain	4.5	3.6
Chest pain	1.8	1.2
Neck pain	1.6	1.1
Allergic reaction	1.5	0.8
CARDIOVASCULAR SYSTEM		
Tachycardia	2.6	0.6
Vasodilation	2.4	0.9
Migraine	2.4	2.0
Hypertension/increased blood pressure	2.1	0.9
Palpitation	2.0	0.8
DIGESTIVE SYSTEM		
Anorexia	13.0	3.5
Constipation	11.5	6.0
Increased appetite	8.7	2.7
Nausea	5.9	2.8
Dyspepsia	5.0	2.6
Gastritis	1.7	1.2
Vomiting	1.5	1.4
Rectal disorder	1.2	0.5
METABOLIC & NUTRITIONAL		
Thirst	1.7	0.9
Generalized edema	1.2	0.8
MUSCULOSKELETAL SYSTEM		
Arthralgia	5.9	5.0
Myalgia	1.9	1.1
Tenosynovitis	1.2	0.5
Joint disorder	1.1	0.6
NERVOUS SYSTEM		
Dry mouth	17.2	4.2
Insomnia	10.7	4.5
Dizziness	7.0	3.4
Nervousness	5.2	2.9
Anxiety	4.5	3.4
Depression	4.3	2.5
Paresthesia	2.0	0.5
Somnolence	1.7	0.9
CNS stimulation	1.5	0.5
Emotional lability	1.3	0.8
RESPIRATORY SYSTEM		
Rhinitis	10.2	7.1
Pharyngitis	10.0	8.4
Sinusitis	5.0	2.6
Cough increase	3.8	3.3
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SKIN & APPENDAGES		
Rash	3.8	2.5
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Herpes simplex	1.3	1.0
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SPECIAL SENSES		
Taste perversion	2.2	0.8
Ear disorder	1.7	0.9
Ear pain	1.1	0.7
UROGENITAL SYSTEM		
Dysmenorrhea	3.5	1.4
Urinary tract infection	2.3	2.0
Vaginal moniliasis	1.2	0.5
Metrorrhagia	1.0	0.8

The following additional adverse events were reported in ≥1% of all patients who received MERIDIA in controlled and uncontrolled pre-marketing studies.

Body as a Whole: fever.

Digestive System: diarrhea, flatulence, gastroenteritis, tooth disorder.

Metabolic and Nutritional: peripheral edema.

Musculoskeletal System: arthritis.

Nervous System: agitation, leg cramps, hypertonia, thinking abnormal.

Respiratory System: bronchitis, dyspnea.

Skin and Appendages: pruritus.

Special Senses: amblyopia.

Urogenital System: menstrual disorder.

Postmarketing Reports: Voluntary reports of adverse events temporally associated with the use of MERIDIA are listed below. It is important to emphasize that although these events occurred during treatment with MERIDIA, they may have no causal relationship with the drug. Obesity itself, concurrent disease states/risk factors, or weight reduction may be associated with an increased risk for some of these events.

abnormal dreams, abnormal ejaculation, abnormal gait, abnormal vision, alopecia, amnesia, anaphylactic shock, anaphylactoid reaction, anemia, anger, angina pectoris, arthrosis, atrial fibrillation, blurred vision, bursitis, cerebrovascular accident, chest pressure, chest tightness, cholecystitis, cholelithiasis, concentration impaired, confusion, congestive heart failure, depression aggravated, dermatitis, dry eye, duodenal ulcer, epistaxis, eructation, eye pain, facial edema, gastrointestinal hemorrhage, Gilles de la Tourette's syndrome, goiter, heart arrest, heart rate decreased, hematuria, hyperglycemia, hyperthyroidism, hypesthesia, hypoglycemia, hypothyroidism, impotence, increased intraocular pressure, increased salivation, increased urinary frequency, intestinal obstruction, leukopenia, libido decreased, libido increased, limb pain, lymphadenopathy, manic reaction, micturition difficulty, mood changes, mouth ulcer, myocardial infarction, nasal congestion, nightmares, otitis externa, otitis media, petechiae, photosensitivity (eyes), photosensitivity (skin), respiratory disorder, serotonin syndrome, short term memory loss, speech disorder, stomach ulcer, sudden unexplained death, supraventricular tachycardia, syncope, thrombocytopenia, tinnitus, tongue edema, torsade de pointes, transient ischemic attack, tremor, twitch, urticaria, vascular headache, ventricular tachycardia, ventricular extrasystoles, ventricular fibrillation, vertigo, yawn.

Other Notable Adverse Events: ***Seizures:*** Convulsions were reported as an adverse event in three of 2068 (0.1%) MERIDIA treated patients and in none of 884 placebo-treated patients in placebo-controlled premarketing obesity studies. Two of the three patients with seizures had potentially predisposing factors (one had a prior history of epilepsy; one had a subsequent diagnosis of brain tumor). The incidence in all subjects who received MERIDIA (three of 4,588 subjects) was less than 0.1%.

Ecchymosis/Bleeding Disorders: Ecchymosis (bruising) was observed in 0.7% of MERIDIA treated patients and in 0.2% of placebo-treated patients in pre-marketing placebo-controlled obesity studies. One patient had prolonged bleeding of a small amount which occurred during minor facial surgery. MERIDIA may have an effect on platelet function due to its effect on serotonin uptake.

Interstitial Nephritis: Acute interstitial nephritis (confirmed by biopsy) was reported in one obese patient receiving MERIDIA during pre-marketing studies. After discontinuation of the medication, dialysis and oral corticosteroids were administered; renal function normalized. The patient made a full recovery.

Altered Laboratory Findings: Abnormal liver function tests, including increases in AST, ALT, GGT, LDH, alkaline phosphatase and bilirubin, were reported as adverse events in 1.6% of MERIDIA-treated obese patients in placebo-controlled trials compared with 0.8% of placebo patients. In these studies, potentially clinically significant values (total bilirubin ≥2 mg/dL; ALT, AST, GGT, LDH, or alkaline phosphatase ≥3x upper limit of normal) occurred in 0% (alkaline phosphatase) to 0.6% (ALT) of the MERIDIA treated patients and in none of the placebo-treated patients. Abnormal values tended to be sporadic, often diminished with continued treatment, and did not show a clear dose-response relationship.

DRUG ABUSE AND DEPENDENCE: Controlled Substance: MERIDIA is controlled in Schedule IV of the Controlled Substances Act (CSA).

Abuse and Physical and Psychological Dependence: Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., drug development of tolerance, incrementation of doses, drug seeking behavior).

OVERDOSAGE: Human Experience: Three cases of overdose have been reported with MERIDIA. The first was in a 2-year-old child of one patient who ingested up to eight 10 mg capsules. No complications were observed during the overnight hospitalization, and the child was discharged the following day with no sequela. The second report was in a 30-year-old male in a depression study who ingested approximately 100 mg of sibutramine in an attempt to commit suicide. The patient suffered no adverse effects or ECG abnormalities post-ingestion. The third report was in the 45-year-old husband of a patient in an obese dyslipidemic study. He ingested 400 mg of his wife's drug supply and was hospitalized for observation; a heart rate of 120 bpm was noted. He was discharged the next day with no apparent sequelae.

Overdose Management: There is no specific antidote to MERIDIA. Treatment should consist of general measures employed in the management of overdosage: an airway should be established; cardiac and vital sign monitoring is recommended; general symptomatic and supportive measures should be instituted. Cautious use of β-blockers may be indicated to control elevated blood pressure or tachycardia. The benefits of forced diuresis and hemodialysis are unknown.

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Annals of Internal Medicine | SUMMARIES FOR PATIENTS

Factors Associated with *Helicobacter pylori* Infections in the United States That Are Resistant to Usual Antibiotics

Summaries for Patients are a service provided by *Annals* to help patients better understand the complicated and often mystifying language of modern medicine.

The full report is titled "Risk Factors for *Helicobacter pylori* Resistance in the United States: The Surveillance of *H. pylori* Antimicrobial Resistance Partnership (SHARP) Study, 1993–1999." It is in the 1 January 2002 issue of *Annals of Internal Medicine* (volume 136, pages 13-24). The authors are JM Meyer, NP Silliman, W Wang, NY Siepman, JE Sugg, D Morris, J Zhang, H Bhattacharyya, EC King, and RJ Hopkins.

What is the problem and what is known about it so far?

Helicobacter pylori is a type of bacteria that can cause stomach ulcers. Infection with *H. pylori* is usually successfully treated with a combination of several antibiotics. However, some *H. pylori* bacteria are able to grow despite treatment with the usual antibiotics. Such bacteria are "antibiotic resistant." If doctors knew the information that predicts when a patient will be resistant to treatment, they could be alert for possible resistance before they treat a patient who is at high risk for infection by resistant bacteria. However, no one has fully described what characteristics place patients at risk for *H. pylori* resistance.

Why did the researchers do this particular study?

To estimate how frequently antibiotic-resistant *H. pylori* infection occurs in the United States and to identify factors associated with resistance.

Who was studied?

The researchers studied 3624 patients with *H. pylori* infection who had participated in 1 of 20 studies of treatment of *H. pylori* infection.

How was the study done?

The researchers of the present study contacted the researchers who led the 20 past studies and collected information on whether each patient's infection was resistant to any of three antibiotics (clarithromycin, metronidazole, and amoxicillin). They also collected patients' characteristics, such as age, state of residence, sex, ethnicity, presence or past occurrence of a stomach ulcer, and method used to test for *H. pylori*. They then calculated the frequency of resistant *H. pylori* infection and searched for associations between the patient characteristics and resistance to antibiotics.

What did the researchers find?

Overall, 10% of infections were resistant to clarithromycin, 37% were resistant to metronidazole, and 1% were resistant to amoxicillin. Patients who lived in the northeastern or mid-Atlantic regions of the United States, were older, were women, and had no active ulcer were more likely to have resistance to clarithromycin than patients without these factors. Patients who were women, Asian, or were in 1 of the 20 included studies in the earlier 1990s were most likely to have metronidazole resistance. Amoxicillin resistance was very infrequent and was not associated with any patient characteristics.

What were the limitations of the study?

Resistance patterns for bacteria vary over time, so it is not known whether these results, which were based on data from 1993 to 1999, apply to current times. This study also does not tell us whether knowing that these patients were at risk for resistance would have improved their outcomes.

What are the implications of the study?

Doctors should consider the factors identified to be associated with clarithromycin and metronidazole resistance. When a patient has these factors, doctors may choose to test for resistance or prescribe an alternate antibiotic treatment for *H. pylori*.

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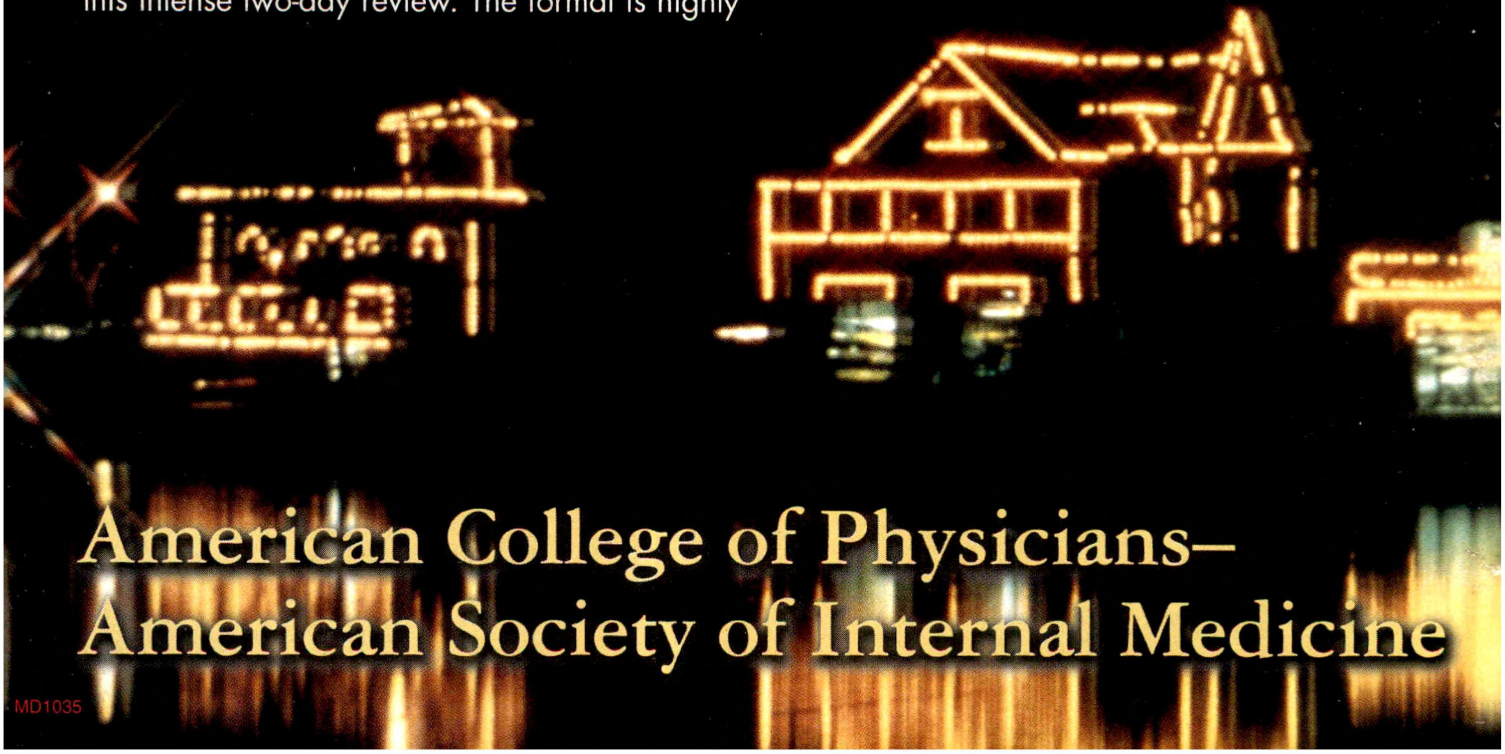

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Annals of Internal Medicine | SUMMARIES FOR PATIENTS

Recovery Rate and Prognosis in Older Persons Who Develop Acute Lung Injury and the Acute Respiratory Distress Syndrome

Summaries for Patients are a service provided by *Annals* to help patients better understand the complicated and often mystifying language of modern medicine.

The full report is titled "Recovery Rate and Prognosis in Older Persons Who Develop Acute Lung Injury and the Acute Respiratory Distress Syndrome." It is in the 1 January 2002 issue of *Annals of Internal Medicine* (volume 136, pages 25-36). The authors are EW Ely, AP Wheeler, BT Thompson, M Ancukiewicz, KP Steinberg, and GR Bernard, for the Acute Respiratory Distress Syndrome Network.

What is the problem and what is known about it so far?

Elderly people are much more likely to develop respiratory failure and require the use of a respirator than younger people. On the other hand, the results of respirator use in the elderly do not appear to be as good as in younger people, but the exact relationship between age and outcome is uncertain. The National Heart, Lung, and Blood Institute (NHLBI) sponsored a large study on acute lung injury that leads to respiratory failure. The data were made available to other researchers for further analysis.

Why did the researchers do this particular study?

To find out how advancing age affects survival from acute lung injury and whether recovery takes longer in older patients.

Who was studied?

902 patients at 24 U.S. hospitals who participated in the NHLBI study between 1996 and 1999. Patients were included in the study if they had acute lung injury requiring use of a respirator, had low oxygen levels, and had a chest x-ray indicating that the respiratory problem was not due to heart failure. Of the participants, 729 were younger than 70 years of age and 173 were 70 years of age or older.

How was the study done?

Patients were evaluated each day to see if a respirator was still needed. Depending on the results of these evaluations, patients were allowed to breathe on their own for 5 minutes; if they did well, additional time off the respirator was prescribed and respiratory assistance was eventually discontinued. The time required to reach each landmark of recovery was recorded, as were the length of stay in the intensive care unit and the survival rate.

What did the researchers find?

Seventy percent of the younger patients and 40% of the older patients were discharged from the hospital alive within the first 180 days. At the time of entry into the study, the severity of lung injury was similar in both age groups. Older patients needed the respirator longer, were more likely to require reinstitution of respirator therapy after initial improvement, and stayed in the intensive care unit longer than younger patients. At 28 days after initiation of respirator use, the survival rate was lower with each decade of advancing age.

What were the limitations of the study?

Several nonrespiratory health problems (such as brain abnormalities) were not carefully monitored but could have affected the results. In addition, older patients may have been more likely than younger patients to have had life support withdrawn because of poor general condition. Furthermore, preexisting illness was difficult to take into account in interpreting the results.

What are the implications of the study?

Although elderly patients seem to recover initially from acute lung injury at a rate similar to younger patients, they are more likely to return to mechanical ventilation and are more likely to die of their acute lung illness. Age alone should not be used as a criterion to deny respirator care. Rather, more effort should be made to improve outcomes in elderly people who develop acute lung failure.

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Annals of Internal Medicine | SUMMARIES FOR PATIENTS

Blood Clots and Abnormal Vessels of the Inferior Vena Cava

Summaries for Patients are a service provided by *Annals* to help patients better understand the complicated and often mystifying language of modern medicine.

The full report is titled "Anomalies of the Inferior Vena Cava in Patients with Iliac Venous Thrombosis." It is in the 1 January 2002 issue of *Annals of Internal Medicine* (volume 136, pages 37-41). The authors are A Obernosterer, M Aschauer, W Schnedl, and RW Lipp.

What is the problem and what is known about it so far?

Blood containing oxygen and vital nutrients is pumped to various parts of the body through blood vessels called arteries. After the body absorbs the oxygen and nutrients, blood returns to the heart and lungs through blood vessels called veins. Deep veins in the legs and pelvis join to form a large vein in the back of the abdomen (inferior vena cava), which carries blood from the lower part of the body to the heart. (The inferior vena cava is usually a single large vein that forms from many smaller veins in the early stages of development of a human embryo.) Sometimes adults get blood clots in their veins, a condition known as deep venous thrombosis. The blood clots usually form in the veins of the calves and the thighs, but they occasionally occur in the veins in the pelvis. Inferior vena cava vessels that developed abnormally might increase the risk for blood clots in the pelvic veins, but no one has any proof that this idea is correct.

Why did the researchers do this particular study?

The researchers wanted to see whether adults with clots in the deep veins of their legs and pelvis have abnormal inferior vena cava vessels.

Who was studied?

The researchers studied 97 adults with blood clots in the deep veins of their legs.

How was the study done?

The adults had special sound wave tests (duplex ultrasonography) to detect blood clots and abnormal blood flow in their veins. If ultrasonography showed clots in the veins of the pelvis, the patients had special x-ray dye tests (ascending venography) to examine their inferior vena cava vessels. If the venograms showed no blood flow through the inferior vena cava, the patients underwent a special computer-assisted imaging technique (magnetic resonance imaging [MRI]) to show detailed images of the anatomy of the inferior vena cava.

What did the researchers find?

Thirty-one of the 97 patients with blood clots in their legs also had blood clots in their pelvic veins. The anatomy of the inferior vena cava vessel was abnormal in 5 of the 31 patients who had pelvic vein clots. The average age of the 5 adults with abnormal inferior vena cava vessels was 25 years. The average age of the other 92 people was 53 years. Two of the 5 people with abnormal inferior vena cava vessels had repeated episodes of blood clots in their legs or pelvis.

What were the limitations of the study?

The study involved adults who were referred to radiology for special tests that look for blood clots. There may be people with abnormal inferior vena cava vessels who either do not develop blood clots or do not get tested for blood clots. Thus, this study cannot tell us how often abnormal inferior vena cava vessels are actually associated with blood clots.

What are the implications of the study?

Physicians should suspect abnormal inferior vena cava vessels when an adult younger than 30 years of age has blood clots in the veins of the pelvis. Such adults may have high risk for repeated episodes of blood clots.

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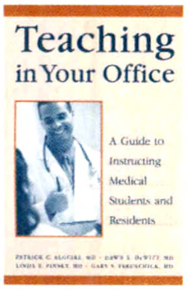

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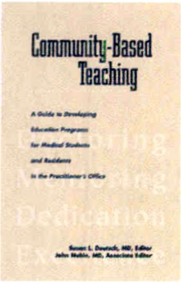

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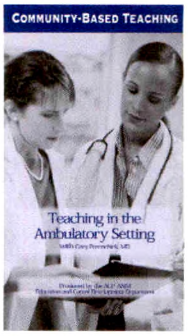

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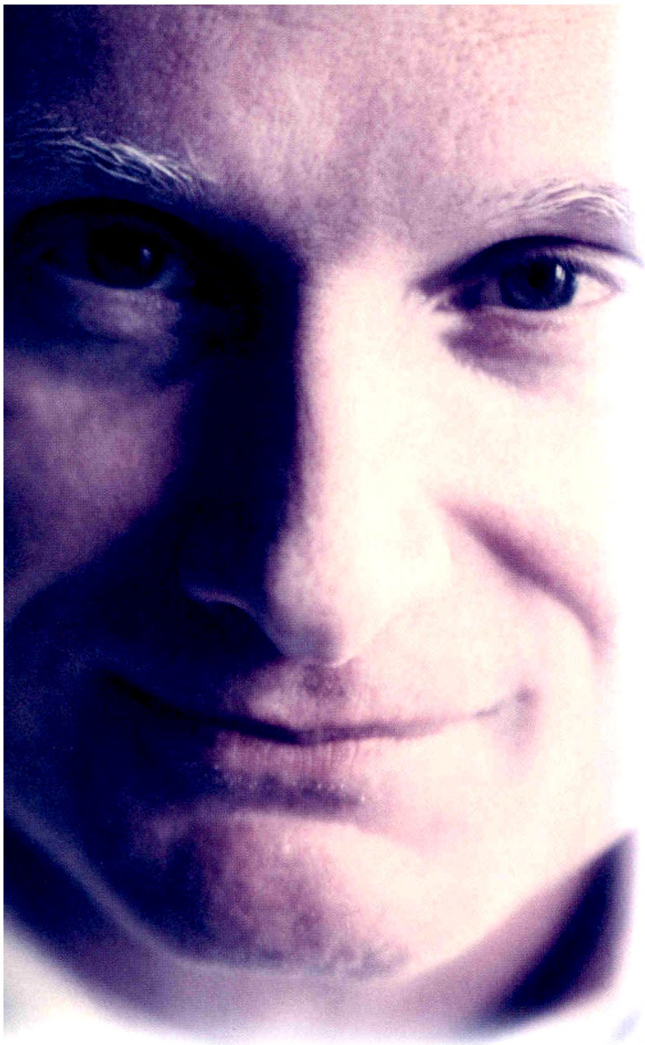

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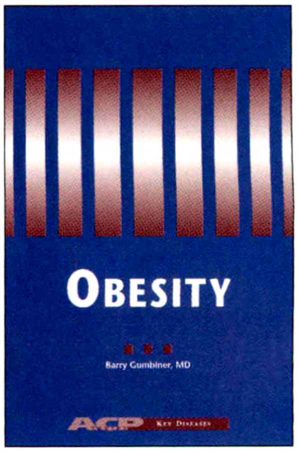

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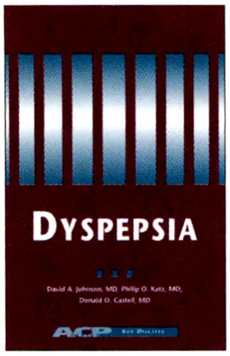
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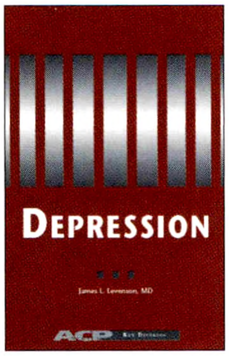

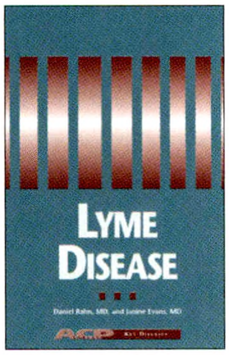

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Orders for physician service advertising must be submitted in writing. Although the American College of Physicians-American Society of Internal Medicine (ACP-ASIM) believes the advertisements in these pages to be from reputable sources, ACP-ASIM does not investigate the offers made and assumes no liability concerning them. Acceptance of advertising is geared to products and services that assist physicians in their practices. ACP-ASIM reserves the right to decline, withdraw, or edit advertisements.

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This site offers an interactive clinical research textbook suitable for courses or individual self-study by beginning or advanced researchers, guides to grant opportunities, and more.

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Annals of Internal Medicine

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Classified advertising in *Annals* is the most effective way to reach internists. By placing your advertisement in any issue of *Annals of Internal Medicine,* your classified ad will also appear on ACP-ASIM Online, the website of the American College of Physicians–American Society of Internal Medicine, at no additional *space charge.* For a nominal processing fee your ad will appear on ACP-ASIM's Website approximately 2 weeks before the print publication and remain on ACP-ASIM Online for a total of 4 weeks. Stand-alone advertisement options are also available. Visit ACP-ASIM Online at **www.acponline.org/careers.**

Advertisements are classified according to the major categories listed below. If you do not indicate the classification, we will determine the most appropriate category. Classifieds are divided into **state or region** by subhead. Please indicate both the classification and subhead under which your ad should appear.

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Specialties and Subspecialties:

Internal Medicine and Primary Care
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A "word" is one or more letters, numbers, or special characters bound by spaces.

Example:

Cardiology-Internist = 1 word
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Bold typeface available for $35 fee. (Entire ad must be bold typeface).

Example:

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This advertisement is 45 words at $4.15 per word: it costs $186.75. Because a Box is requested there is an additional charge of $25.00 for each insertion. The total price is therefore $211.75 for one insertion of the ad.

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Box numbers are available for an additional $25.00 per insertion. "Respond to Box AIM" counts as four words. We will not reveal any information regarding the advertiser. Responses will be forwarded via first class mail.

Replies to a Box number should be sent to *Annals of Internal Medicine,* 190 North Independence Mall West, Philadelphia, PA 19106-1572. Be sure to include the Box number on the envelope. Replies may not exceed one ounce.

2002 Issue and Closing Dates

Issue Date	Deadline Date	Issue Date	Deadline Date	Issue Date	Deadline Date
Jan. 1	Dec. 1	May 7	April 1	Sept. 3	Aug. 1
Jan. 15	Dec. 15	May 21	April 15	Sept. 17	Aug. 15
Feb. 5	Jan. 1	June 4	May 1	Oct. 1	Sept. 1
Feb. 19	Jan. 15	June 18	May 15	Oct. 15	Sept. 15
March 5	Feb. 1	July 2	June 1	Nov. 5	Oct. 1
March 19	Feb. 15	July 16	June 15	Nov. 19	Oct. 15
April 2	March 1	Aug. 6	July 1	Dec. 3	Nov. 1
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ALL E-MAILED OR FAXED ADVERTISEMENTS MUST BE RECEIVED BEFORE 10 AM ON THE DEADLINE DATE. Any advertisements received after that time will be inserted in the next issue. When confirming your faxed advertisements by mail, please mark the date your advertisement was faxed to avoid duplication. Our fax number is **215-351-2686 or 215-351-2685.**

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Internal Medicine and Primary Care

California

The VA Palo Alto Health Care System (VAPHCS), an affiliate of Stanford University School of Medicine, invites applications for physicians in primary care at Livemore, Stockton and Modesto, California. Applicants must be Board-Eligible or Board-Certified in internal medicine or family practice. The department of Veterans Affairs is committed to increasing the representation of women and members of minority groups on its faculty and particularly encourages applications from such candidates. Applicants should send curriculum vitae, a brief statement of their clinical interests and names of three potential references to: Ellen Shibata, M.D. Deputy Chief of Staff (111C), VA Palo Alto Health Care System: Livermore Division; 4951 Arroyo Road, Livermore California, 94550 EOE.
W-IN2N.107.1X

Northern California's Rolling Foothills Outstanding opportunity near Sacramento to establish your own practice with the support of the community hospital or share an office with two practicing internists. Excellent recreation, housing, and schools. Area does not qualify for J-1 Visa. Call 1-888-229-9495. Fax CV to 916-482-1154 or email to wilkinstina@earthlink.net.
W-IN1N.420.TF

Lake Tahoe. BC-BE internist needed to join 3 board certified internists in primary care group. Successful, established practice. Low managed care service area. Good call schedule. Offices at modern medical center with excellent on-site outpatient services. Well-equipped acute care hospital. Highly competitive income and benefits are offered. Easy access to Reno, Sacramento, and San Francisco. Magnificent natural beauty. Relaxed lifestyle with diverse recreational advantages. Send CV in confidence or call Sharon MacKenzie 800-735-4431; Fax 707-824-0146; e-mail mackenz@sonic.net.
W-IN1N.534.TF

Connecticut

Hartford-Suburban. BC-BE internist to replace retiring physician July, 2002. Competitive salary and benefits. Liberal on-call rotation. Respond to Box AIM 135N.
W-IN1N.785.2X

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Idaho

Southern Idaho: Intermountain Health Care (IHC) is seeking one BC/BE internist for private practice in Burley. Office space is located in the medical office building next to Cassia Regional Medical Senter, a 40-bed IHC facility which opened in 1995. Two year salary guarantee. Share office and expenses with two other internists if desired. Relocation provided. Send/fax CV to: IHC Physician Services, Attn: Wilf Rudert, 36 South State Street, 20th Floor, Salt Lake City, UT 84111, 800-888-3134 #1. Fax: 801-442-2999. E-mail: comdixon@ihc.com. Web: www.ihc.com/phys_recruit.
W-IN1N.678.3X

Indiana

Physicians (Primary Care) Indiana. Do what you were trained to do ... care for patients. No more worries about the constant billing, insurance and staffing that come with running your own practice. Prison Health Services offers a career that is challenging, rewarding, and allows you to do what you do best! We currently have statewide FT opportunities within the Indiana Department of Corrections. Physicians must be BC-BE in a primary care specialty. We offer excellent compensation and benefits. Contact or forward you C.V. to: Mindy Halpern, 800-729-7053, ext. 5502; e-mail: halpermh@asgr.com; fax: 877-729-7053. EEO/AA.
W-IN2N.120.1X

Kentucky

Seeking highly Motivated Board-Eligible certified internist to join a North Shore, Western Suffolk county practice. Send CV to fax 631-499-5367 or e-mail commackdoc@aol.com.
W-IN1N.789.2X

Maryland

Southern Maryland. Solo-practitioner seeks BC or BE, internal medicine physician (practicing 5 years or less) to join her 100% fee-for-service practice. Competitive salary and benefits. Physician call 1:3. Lovely, family-friendly area that offers city amenities (25 miles south of Washington, DC) and pristine beauty. Contact: Michele Santiago, fax 301609-4470, or mail to P.O. Box 1070, La Plata, MD 20646.
W-IN2N.101.1X

Send box Replies To:

Reply Box AIM-XXX
Annals of Internal Medicine
190 N. Independence Mall W.
Sixth Street at Race
Philadelphia, PA 19106

Minnesota

Minnesota. Join three BC internist in a 25 physician MS group in Fairmont, a scenic and safe community with 5 recreational lakes, affordable homes and award winning schools. We seek a BE/BE internist for an inpatient/outpatient practice. Subspecialty interests in pulmonology and/or geriatrics is welcomed. We are the only primary care, multispecialty, and hospital practice in town of 14,000 (pop.) with a service area of 40,000. We offer an excellent salary + production compensation, comprehensive fringe benefit package and the subspecialty resources of Mayo Clinic. Contact: Michael Griffin or Larry Gleason toll free phone 888-577-5660, email: griffin.michael@mayo.edu or gleason.larry@mayo.edu, website: www.mhs,mayo.edu, fax: 507-284-4511.
W-IN1N.742.1X

Montana

Enjoy the Mountains of Western Montana. St. Peter's Hospital (a 99-bed hospital) is seeking a BC-BE internist for a well-established internal medicine group with 1:5 call. Includes income guarantee and relocation. Helena, Montana offers a wide array of cultural amenities, and great outdoor opportunities such as fly fishing, hiking, water sports, skiing, & mtn. biking right out your front door. Helena is the ideal location to raise a family. Not a J-1 site. Contact Kacey Askin, 406-447-2559 or fax CV to 406-447-2609, E-mail at kaskin@stpetes.org, or visit www.stpetes.org for more information.
W-IN2N.105.1X

St.Louis/Missouri. This 538 bed hospital seeks an urgent care physician to work in 21-bed emergency department. Annual volume of 35,000. High number of challenging and unique medical cases with a 40% admission rate. Requires B/C in internal medicine. Excellent compensation package including benefits. Contact: Rita Offenberg, InPhyNet, A Team Health Affiliate 1-800-424-3672, ext. 2906; Fax 954-424-3270.
W-IN2N.112.1X

Seeking General Internist to join growing eight-internist/multispecialty practice. University community with ready access to mountains, skiing, fly-fishing and Yellowstone Park. BC-BE required. Send CV with cover letter to Sandi Kramer, 931 Highland Boulevard, Suite 3220, Bozeman, MT 59715. Email imab@in-tch.com. Fax 406-587-3610. This is not a J-1 Visa, HPSA or MUA site.
W-IN2N.104.1X

Montana. You've Earned It. Things are different here. We have the technology and personnel to help your practice grow and patients who need and appreciate your skills. The Great Falls Clinic is seeking a BC-BE internist for a rapidly expanding 100+ provider, multispecialty organization. We offer a benefit package and salary leading to partnership. If interested, send CV and professional goals to: Jeff Hinz; M.D., Medical Director, PO Box 5012, Great Falls, MT 59403. E-mail: jeff.hinz@gfclinic.com.
W-IN2N.108.1X

Internal Medicine and Primary Care *continued*

New Hampshire

Excellent Opportunity For B/C General Internist to join group practice. Easy access to Dartmouth, Boston, ski areas, whitewater, lakes. Salary with incentive and benefits. No J-1/H1-B site. Contact Susan Edson: Telephone 207 866-5680, Fax 207-866-5696, sedson codenum:W-IN1N.781.3X

New Jersey

Internist. Medical director - housestaff teaching practice, 50% teaching, 25% private patients, 25% residency administration. Send CV to Patty Bono, 55 phyldan RD\d., E.Hanover, NJ 07936.
W-IN1N.790.3X

New Mexico

New Mexico BC-BE general internist needed by group of five due to continued strong growth. Excellent practice opportunity, both outpatient/inpatient. Community repeatedly selected as one of nation's top small town retirement communities. World class weather, college town, in mountains adjacent to Gila Wilderness. No J-1 opportunities. CV to James Skee, M.D, Silver Internal Medicine, 1600 32nd, Silver City, NM 88061.
W-IN1N.753.3X

North Carolina

We Have an Established Practice to offer a BE-BC internist. Gastonia, NC is a town of 50,000+ just West of Charlotte. Busy private practice with 4 BC IM with GI cardiology subspecialties. Great new facility located adjacent to hospital campus. Competitive salary and benefits. CV can be sent to: fax 704-867-0738, email ghthomas@gastonmedicalgroup.com, or emailed to 660 Summit Crossing Place, Gastonia, NC 28054, Attn: GH Thomas.
W-IN1N.714.3X

Full-Time General Internist, Board-certified to join well- established group in Hendersonville, NC. Beautiful mountain community. Low HMO penetration. First-rate, debt-free hospital. One in 15 call schedule. Large retiree population with plenty of work to do. Tired of contract hassles? Call us...We are running our own business. Contact rosa@q-h-a.net, or call 828-693-3193.
W-IN1N.561.2X

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Ohio

Northeast Ohio - Louis B. Stokes Cleveland VA Medical Center's teaching affiliate of Case Western University (CWRU) is seeking quality applicants for full-time internal medicine/geriatric positions in expanding primary-care network throughout Northeast Ohio, including Akron, Brecksville, Canton, Painesville, Youngstown, New Philadelphia, Ravenna, Warren, East Liverpool, McCafferty, Mansfield and Sandusky/Lorain. The primary responsibilities are providing ambulatory patient care in a multidisciplinary setting with teaching and research opportunities. Competitive salary and comprehensive benefits package. Send CV to: Scott K. Ober, MD, MBA, 10701 East Blvd, Cleveland. OH 44106. Fax 216-231-3289. EOE No J-1 opportunities.
W-IN2N.119.2X

Southwest Ohio. BC-BE internist needed to join busy primary care group in semi-rural community. Easy access to Cincinnati, Dayton and Columbus. Excellent local hospital, currently undergoing expansion. Mail resume: Administrator, Wilmington Medical Associates, 1184 W. Locust, Wilmington, OH 45177; fax: 937-382-7877; or e-mail: tecoomer@aol.com.
W-IN1N.787.3X

Oregon

General Internist, Great opportunity with stable, growing, physician owned multispecialty group in Willamette Valley, Oregon. First year salary guaranteed. Cannot support J-1 visa. Contact Administrator, 503-391-1110, Fax 503-370-4237, email: Copleyp.@drsclinic.com.
W-IN1N.710.1X

Tremendous opportunity in Oregon's Scenic Willamette Valley. Busy five physician, internal medicine group seeking full time BC-BE internist to join well established practice in Springfield OR. Call 1/5, guaranteed salary/benefits with partnership opportunity at one year. Not a J-1 visa service area. Contact Vicki Gray at 541-762-2176 or vgray@lipa.net.
W-IN1N.771.3X

Southern Oregon. Looking for BC-BE internist to join 10-physician IM department in a physician-owned, financially healthy multispecialty group with 50-year history. First year salary guarantee plus incentive bonus. Beautiful southern Oregon community of 20,000 serving region of 80,000. Region offers Shakespeare festival and famous Rogue River for rafting, fishing, and other outdoor activities. Send CV to Administrator, Grants Pass Clinic, LLP, 125 NE Manzanita, Grants Pass, OR 97526; or call, telephone 541-472-5502; fax 541-472-5671.
W-IN0N.616.TF

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Pennsylvania

Northwestern Pennsylvania - Erie. Full-time BC internist sought to join our dynamic, growing group in this beautiful lake region. Position includes both inpatient care, with some teaching available. Affiliated with Hamot Medical Center, a 467-bed tertiary care hospital ranked one of the "100 Top Hospitals in America". Residency training programs at Hamot include Family Practice and Orthopaedics, and Erie is home to local medical school. High earning potential (top 10% of the country for general internists), great benefits with over 6 weeks off per year. Excellent call schedule. Erie, Pennsylvania, is a safe, friendly, family-oriented city with excellent schools, beautiful beaches and many recreational and cultural amenities. Send CV to Patricia Rybak: fax 814-877-5696, E-mail: patty.rybak@hamot.org, call: 814-877-2517. No J-1 positions.
W-IN1N.770.3X

Wanted. Internist or Cardiologist to join a solo internal medicine/cardiology practice located in under-served area close to metropolitan Pittsburgh, PA. Call 724-378-3440 or fax resume to 724-375-1005.
W-IN1N.797.2X

South Carolina

Internist W/WO Subspecialty. Outstanding private practice opportunity to associate with two University-Trinidad double-boarded internists with subspecialty in ID and allergy in a highly desirable small southeastern city. Hospital and office-based practice. Salary guarantee and benefits. Outstanding income potential. University town with excellent living and recreational opportunities. Send CV to Internal Medicine Associates Box 5238 Aiken SC 29804.
W-IN1N.780.3X

Texas

East Texas. Seeking BC-BE internist to join busy, established practice. State-of-the-are, integrated facility. Interest in procedures and/or non-invasive cardiology a plus. Call 1:5. Salary, signing bonus, benefits. Great climate, exceptional lifestyle - easy access to Dallas. Contact Jane Vogt at 800-449-7116; fax 888-820-7029; e-mail jvogt@cejka.com. ID#20216IA. For more opportunities, visit www.cejka.com.
W-IN2N.102.1X

Outstanding Internal Medicine Opportunity in beautiful Austin, Texas. private practice with hospital support. Enjoy thriving practice while living in one of the top cities in the U.S high quality of life, great schools, University of Texas, hills, lakes, rivers, recreational opportunities, arts, theater, symphony. Brian White, 1-888-339-7444; fax 1-509-695-5956; em bwhite@compuwise.net.
W-IN1N.786.3X

www.acponline.org/careers

Internal Medicine and Primary Care *continued*

Utah

Intensivists, Northern Utah: McKay-Dee Hospital, a tertiary care facility, is seeking additional intensivists to staff their new state-of-the-are facility. The positions are full-time, salaried, hospital-based. The responsibilities are 80% clinical and 20% CQI/Clinical Research. Generous benefits package and competitive salary. The Ogden/Salt Lake City area was ranked as the best place to live in North America in the sixth edition of places rated almanac. In addition, Utah has been named #5 "Most Livable State" by Morgan Quitno Press. Ogden is located a the foothills of the Wasatch Mountains, site of the 2002 Winter Olympics. Applicants must be BC-BE in critical care medicine. Send/fax CV to IHC Physician Svcs., 36 S. State St., 20th Floor, Salt Lake City, UT 84111. 800-888-3134 #1. Fax: 801-442-2999. E-mail: comdixon@ihc.com. Web: www.ihc.com/phys_recruit.
W-IN1N.773.2X

Vermont

Vermont. BC-BE internist to join established internist in west central VT. 15 miles from 2nd largest hospital with full complement of specialty coverage. Family environment in charming New England community near lakes and mountains, with four season recreational opportunities. Enjoy nearby Killington Ski Resort. Good call coverage. Competitive salary with full benefits and incentive program. Send CV to Rebecca Banco, Rutland Regional Medical Center, 160 Allen Street, Rutland, VT 05701, fax 802-747-6207, via e-mail bbanco@rrmc.org, or call 802-747-3844. (Not eligible for J-1 Visa program.)
W-IN1N.543.3X

Washington

Bellingham, WA BC-BE internal Medicine opportunity for a director of a newly formed hospital-affiliated geriatric center. Responsible for providing consultative and primary geriatric care and oversee the development community focused geriatric assessment programs. desire training, interest and background in the field of geriatrics. Required expertise in clinical management of geriatric patients and medical staff. Coastal college comment in a moderate sized city located in the beautiful northwest region on Puget Sound in Washington State. Please reply with cover letter and CV to: Kevin Malee, St. Joseph Hospital, 2901 Squalicum Parkway, Bellingham, Washington 98225 or Fax 360-756-4826 or email to: kmalee@peacehealth.org.
W-IN2N.117.2X

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BE-BC General Internal Medicine physician to join thriving, 60-member multispecialty group committed to quality, compassionate care. Enjoy competitive income, favorable call, collegial atmosphere and beautiful facility. Located in lovely, family-friendly Longview, Washington. Mountains, beaches and downtown, Portland, Oregon are all less that one hour away. Contact Anne Bennett, Phone: 360-414-7596 Fax: 360-414-7550 or ABennett@PeaceHealth.org www.PeaceHealth.org.
W-IN2N.127.3X

Wisconsin

Madison, Wisconsin. Excellent opportunity with the University of Wisconsin Medical Foundation. We are seeking a full-time Internal Medicine physician to join four others (28 total IM) at our Madison East Towne Clinic. Teaching opportunities with medical students and residents. Madison is the State Capital and recognized as one of the top cities in which to live and work. Competitive salary and comprehensive benefits package. Contact Laura Schowalter, Director of Physician Recruitment, toll-free 888-267-77764; local 608-287-2561; Fax 608-287-2199. E-mail: laura.schowalter@uwmf.wisc.edu. EO/AA Employer. Unless confidentiality is requested in writing, information regarding the applicants must be released upon request. Finalists cannot be guaranteed confidentiality.
W-IN1N.751.1X

Wyoming

General Internal Medicine, exceptional practice opportunity for a general internist to join group of 11 general and subspecialty internists. A strong work ethic and dedication to excellence are most important. We offer a generous salary and benefits package, minimal managed care, no state income tax and early partnership. A comfortable call schedule allows enjoyment of this Rocky Mountain region. No J-1 visa. Send personal letter and CV to Internal Medicine Group 2301 House Ave., Suite 300, Cheyenne, WY 82001.
W-IN1N.799.3X

National

Pacific Northwest, California and Nationwide. Specialist and Primary Care Physicians needed. Call Chris Warner, PantherEnterprises.com, Physician Recruiting, 800-235-7601, E-mail: Panther@seanet.com, www.PantherEnterprises.com.
W-IN0N.457.TF

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Northwest

Pacific Northwest. Group Health Permanente, a well-established physician owned and managed medical group with primary care and consultative services throughout Washington State, is seeking internists for both inpatient and outpatient services. Glorious northwest setting features breathtaking mountain and water views, easy access to cultural events, museums, professional sports areans, and out door adventures in the San Juan Islands, the Cascade mountains and on the slopes of magnificent Mount Rainier. Great community and quality lifestyle are enhanced by GHP'S competitive salary and top-notch benefits package. To learn more about these exciting opportunities, call 800-543-9323 or visit our website at www.ghc.org. E-mail CV and cover letter to ghprecruiting@ghc.org or fax to 206-448-6191. Equal opportunity employer. No J-1 opportunities.
W-IN2N.106.1X

Cardiology

New York

Cardiology—Westchester County NY. Premier, dynamic, private practice 75-MD multispecialty group seeks BC-BE cardiologist. Collegial and professionally stimulating practice environment. Excellent financial opportunity. Highly desirable Northern Westchester County, NYC suburbs, great schools. Join 2 BC cardiologist in a fully equipped state-of-art-office. Send CV and references to Abe Levy MD, Medical Director. Mount Kisco Medical Group PC. 90 South Bedford Road. Mount Kisco NY 10549-3412. Fax: 914-242-4518.www.mkmg.com.
W-CA2N.116.1X

Endocrinology

Minnesota

Endocrinologist - St. Cloud, Minnesota. Great opportunity for one or two BC-BE endocrinologists to join three endocrinologists in a progressive 131-physican multispecialty clinic with an excellent referral base. Our diabetes program, which will move into a new building in November 2001, was recently recognized by the ADAas a comprehensive diabetes center with certified diabetes educators and dietitians. The clinic practice involves general endocrinology and diabetes with a 1:4-5 call schedule. This growing Central Minnesota community serving a referral area of 575,000 offers an outstanding lifestyle with three colleges, excellent public and private schools and abundant recreational activities. St. Cloud is located in the Mississippi River and is one hour from the Twin Cities or premier lakes area. Attractive compensation and benefits package. Opportunity available for teaching in family practice residency and in surrounding medical communities. Please Contact: Karla Donlin, Physician Recruiter St. Cloud Hospital 1406 Sixth Avenue North St. Cloud, MN 56303 1-800-835-6652 or donlink@centracare.com.
W-EN1N.727.TF

Internal Medicine and Primary Care *continued*

New York

Endocrinology—Westchester County NY. Premier, dynamic, private practice 75-MD multispecialty group seeks second BC-BE endocrinologist. Collegial and professionally stimulating practice environment. Excellent financial opportunity. Highly desirable Northern Westchester County, NYC suburbs, great schools. Send CV and references to Abe Levy MD, Medical Director. Mount Kisco Medical Group PC. 90 South Bedford Road. Mount Kisco NY 10549-3412. Fax: 914-242-4518. www.mkmg.com.
W-EN2N.115.1X

Gastroenterology

Minnesota

St. Cloud, Minnesota. The CentraCare Digestive Center is recruiting a BE-BC gastroenterologist to join a well-established group of 8 gastroenterologists, who will move to the newly constructed CentraCare Health Plaza in November 2001. Therapeutic endoscopic skills and ERCP/ERS training required. EUS training desirable. CentraCare Clinic, a 131-physician, multispecialty clinic with nine clinic locations serving a referral population of 575,000, offers competitive compensation and benefits package. St. Cloud, located 65 miles northwest of Minneapolis/St. Paul on the beautiful Mississippi River in the heart of Minnesota lake country, provides numerous outdoor recreational activities. Three colleges and numerous private and public primary and secondary schools provide excellent educational options for children and adults. Call or send CV to Kristine Cunningham Rose, Physician Recruiter, St. Cloud Hospital, 1406 Sixth Avenue North, St. Cloud, MN 56303. 800-835-6652 ext. 54188, Fax 320-255-5711, E-mail cunninghamrosek@centracare.com, www.centracare.com.
W-GA1N.547.TF

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New York

The Gastrointestinal Oncology Service, Department of Medicine of Memorial Sloan-Kettering Cancer Center is seeking an additional faulty member. The full time position is at the assistant professor level. The gastrointestinal oncology service currently has twelve attending physicians, a busy 21 bed inpatient unit, a highly active inpatient consultative unit, and a large clinical and transitional research program. The successful applicant for this position should have completed a fellowship in medical oncology and have a demonstrated interest in clinical research. Either experience with early Phase I and Phase II trials and/or experience in the use of combined modality therapy with classic chemotherapy or biological response modifiers in association with primary surgery and/or radiation would be useful. Interested applicants should forward a curriculum vitae and bibliography to: David P. Kelsen, M.D. Chief, Gastrointestinal Oncology Service, Memorial Sloan-Kettering Cancer Center 1275 York Avenue, New York, NY 10021. Memorial Sloan-Kettering Cancer Center is an affirmative action, equal opportunity employer.
W-GAIN.797.2X

Geriatrics

Minnesota

St. Mary's/Duluth Clinic Health System is seeking a Geriatrician to join one Geriatrician and 4 NPs in a busy practice. Requirements: BC/BE, FP/IM. Certification of Added Qualification in Geriatric Medicine (CAQ) a plus. SMDC is a 350+ - physician, multispecialty group with more than 20 clinic locations and three hospitals serving a regional population of 460,000 people in northeastern Minnesota, northwestern Wisconsin and upper Michigan. SMDC is the largest, most comprehensive provider of primary, secondary and tertiary health care services in our region Contact: Cathy Ziegler, Physician and Provider Recruitment, 400 East 3rd Street, Duluth, MN 55805, 800-342-1388/ 218-786-3293, Fax: 218-722-9952. E-mail: cziegler@smdc.org Visit our web sites at www.smdc.org or www.duluth.com EOE A/A.
W-GE1N.745.5X

Hospitalists

Arkansas

Arkansas, Little Rock. Great opportunity for internist interested in hospital inpatient care only. Position available July, 2002 Competitive Salary with benefit package. Call Ms. Stewart at 501-660-3245 or 1-800-482 ext. 3245 fgstewart@stvincenthealth.com Not a J-1 position www.stvincenthealth.com.
W-HP1N.743.6X

advertise here

California

Coastal Northern California/Hospitalist. Thriving internal medicine group requires additional BC-BE Internist for 100% Hospitalist practice. Attractive income, benefits and call coverage. Progressive, low managed care medical environment. Safe, coastal community has well-equipped hospital. Excellent schools, university and college. Affordable real estate. Year round mild temperatures. Scenic seaport with large and active arts community. Desirable quality of life. Send CV in confidence or call Sharon Mac Kenzie 800-735-4431; fax 707-824-0146, e-mail mackenz@sonic.net.
W-HP1N.640.TF

Florida

Pensacola Florida. Hospitalist needed for an exciting program at this premiere Pensacola hospital. 9,000 annual admissions. Must be BC-BE in internal medicine. Excellent salary and benefits. Pulmonary experience a plus. Fax CV to Robin Lorber at InPhyNet, at 954-424-3270 or call 800-442-3672, extension 2904.
W-HP2N.111.1X

Outstanding Private Hospitalist Group Needs a 5th physician to join our growing practice. Beautiful South Florida gulf coast community. 100% inpatient work at a 500-bed community hospital system. Strong community and hospital support. No managed care. Guaranteed income with bonus and benefits. Fax CV to: 941-514-8260 or call Gail 941-594-9201.
W-HP2N.103.1X

Hawaii

Seeking a BC-BE Internal Medicine Physician for our new in-house nighttime physician program. Approximately 40-60 hours per week. Kauai Medical Clinic is a 65-physician multispecialty group affiliated with a 181-bed community hospital. Excellent quality of life in a safe, beautiful, rural community. Competitive salary, benefits and relocation package. Sorry, no J-1 Visa position. Send/fax CV to: M. Keyes-Saiki, Kauai Medical Clinic, 3-3420 Kuhio Highway, Suite B, Lihue, HI, 96766-1098. Fax 808-246-1625. Phone 808-246-1621. E-mail: mkeyes-saiki@wilcoxhealth.org.
W-HP2N.121.1X

Montana

Montana. You've Earned it. Things are different. We have the technology and personnel to help your practice prosper and patients who need and appreciate your skills and energies. The Great Falls clinic, LLP is seeking a BC-BE Hospitalist to join our 100+ providers. No outpatient responsibilities. Strong support from 26-member internal medicine department. Hospital resources available. We offer a benefit package and salary leading to partnership. If interested, send CV and professional goals to: Jeff Hinz, M.D., Medical Director, PO Box 5012, Great Falls, MT 59403. E-mail: jeff.hinz@gfclinic.com.
W-HP2N.110.1X

Hospitalists *continued*

New York

Internal Medicine Hospitalist. Westchester County NY. Premier, dynamic, private practice 75-MD Multispecialty group seeks BC-BE internal medicine hospitalist. Collegial and professionally stimulating practice environment. Excellent financial opportunity. Highly desirable Northern Westchester County, NYC suburbs, great schools. Send CV and references to Abe Levy Md, Medical Director. Mount kisco Medical Group PC. 90 South Bedford Road. Mount Kisco NY 10549-3412. Fax: 914-242-4518. www.mkmg.com.
W-HP2N.113.1X

National

IM, All Inpatient (Hospitalists)— 40 hours a week, $120K-$150K, base + bonuses, Earn $175K+. Opportunities in: Florida, North Carolina (Charlotte), New York, Alabama, Georgia, (Central) Tennessee (Nashville), Texas, Virginia (by Richmond), Indiana (South Bend), Missouri, and Kentucky (Lexington), Wisconsin, Washington. Call Mr. Oljace, CEO 888-869-5094 (AIM172).
IN7N.946.1X

Infectious Disease

Colorado

Colorado. BC-BE infectious disease. Seeking associate for busy, 3-physician, 100% ID practice in Denver. Competitive salary and benefits. Practice includes clinical care, outpatient infusion, infection control, antibiotic review. Challenging and interesting cases. Partnership track available. Close proximity to skiing, hiking, mountain biking, and wildlife viewing. Fax CV and letter of interest to 303-777-0786.
ID1N.542.6X

Florida

Central Florida. Seeking BC-BE physician to join established 100% ID practice. Competitive salary and benefits. Mail CV to ID Physician, PO Box 3339, Springhill, FL 34611. W-ID1N.382.2X

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Illinois

The Division of Infectious Disease, Department of Internal Medicine, at Southern Illinois University School of Medicine, Springfield, Illinois, is seeking full time faculty member. Position involves participation in clinical service, teaching and research. Primarily consultative clinical practice comprised of various types of infectious disease, including sexually transmitted diseases, and diseases associated with international travel. Teaching involves medical students in 2nd, 3rd, and 4th years, residents at all levels and fellows in infectious disease. Division has two active research labs with researchers, graduate students and I.D. fellows. Labs also utilized by medical students and residents to conduct research electives. Minimum Qualifications: Graduate of accredited medical school program; Board certified in Internal Medicine; Board-Certified/Board eligible in infectious disease, licensure in state of Illinois or eligible for such. This position has been designated as security sensitive and employment is contingent upon the results of a background investigation. Send resumes to Nancy Khardori, M.D., SIU School of Medicine, P.O. Box 19636, Springfield, IL 62794-9636. For further information, contact Nancy Khardori, M.D. at 217-545-0181. Closing date March 1, 2002 or until filled. SIU School of Medicine is an EO/AA employer.
W-ID2N.100.1X

Maryland

BS-BE Infectious Disease physician needed; private practice (Baltimore). Fax CV 410-225-8062.
W-ID2N.122.6X

Michigan

Michigan: Need infectious disease specialist to join a group of I.D. physicians in private practice in Northwest, beautiful suburbs metropolitan Detroit area (a Motorcity town with many lakes, excellent economy, housing and schools). Well-established and growing practice, in-patient as well as outpatient including infusion center with outstanding supporting staff. Starting salary $150k plus, Full benefit package, an attractive production incentive bonus package. Position to be filled immediately. Fax CV to: 248-626-0880.
W-IDIN.788.5X

Northeast

Pharmaceutical/Biotechnology Industry career opportunities for BC-BE Infectious Disease physicians. Send your CV, "in confidence" to Bruce Rogers Company, Management Consultants, 20 Main Street, Port Washington, NY 11050; 800-942-6663; e-mail: BRUROG-CO@aol.com.
W-ID1N.189.24X

Classified ads on
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Nephrology

Washington

Nephrologist, BE-BC. Thriving 6-member multispecialty group committed to quality, compassionate care seeks third nephrologist. Busy practice with expanding dialysis unit. Expect 50/50 IM/nephrology to start: 70% nephrology within two years. Enjoy exceptional professional and personal lifestyle. Located in lovely, family-friendly Longview, Washington. Mountains, beaches and downtown Portland, Oregon are all less than one hour away. Contact: Anne Bennette, Phone: 360-414-7596 Fax: 360-414-7550 or ABennett@PeaceHealth.org.
W-NP2N.126.3X

Pulmonary Medicine

Maine

Maine. Central Maine Clinical Associates, a growing multispecialty group practice, is seeking a BC-BE pulmonologist with critical care and sleep medicine experience. This exciting opportunity is to join three dedicated pulmonologists/critical specialists in the development of an expanding regional pulmonary practice. A competitive salary and attractive benefits package is offered. Enjoy the professional challenge offered in a sophisticated medical community along with the wonderful recreational opportunities and quality of life in Maine. Send CV to Babette Irwin, Central Maine Medical Center, 300 Main Street, Lewiston, Maine 04240. Fax 207-795-5696, E-mail BIrwin@cmhc.org, or call 800-445-7431. Not a J1 opportunity.
W-PU1N.628.20X

Montana

Montana. You've Earned it. We have the technology and personnel to help your practice prosper and patients who need and appreciate your skills and energies. Great Falls Clinic, LLP is seeking a BC-BE pulmonary or critical care specialist. We offer a benefit package and salary leading to partnership. Does not qualify for J-1 waiver status. Please send CV and professional goals to: Jeff Hinz, M.D., Medical Director, P.O. 5012, Great Falls, MT 59403. E-mail: jeff.hinz@gfclinic.com.
W-PU2N.109.1X

New York

Pulmonary Medicine—Westchester County NY. Premier, dynamic, private practice 75-MD multispeicalty group seeks second BC/BE pulmonary medicine/intensivist, collegial and professionally stimulating practice environment. Excellent financial opportunity. Highly desirable Northern Westchester County, NYC suburbs, great schools. Send CV and references to Abe Levy MD, Medical Director. Mount Kisco Medical Group P.C. 90 South Bedford Road. Mount Kisco NY 10549-3412. Fax: 914-242-4518. www.mkmg.com.
W-PU2N.114.1X

Pulmonary Medicine *continued*

Pulmonary/Critical Care/Internal Medicine BC-BE-Busy hospital/office based 2 physician, triple Boarded practice, on Long Island, minutes from Manhattan and Atlantic Ocean beaches, seeks energetic associate. Competitive salary and incentives leading to early partnership. Part time considered. Reply Box AIM-129N.
W-PU1N.635.6X

North Central

Pulmonologist. Large pulmonary group in Midwest capital city seeking pulmonary/critical care/sleep specialist. Hospital and office-based consultative practice. Interest in sleep medicine desirable but not necessary. Attractive compensation package. Send CV to Reply Box AIM-160B.
PU9N.697.TF

Rheumatology

Colorado

Denver, Colorado Kaiser Permanente Rheumatology: Colorado Permanente Medical Group, P.C., a large multispecialty group serving Kaiser Permanente members, is seeking a BE/BC rheumatologist for an innovative pure subspecialty practice. Major teaching hospital affiliated. Competitive salary and an excellent benefit package. Denver has abundant four-season outdoor activities enhanced by many community amenities. If interested please contact Physician Recruitment, at Colorado Permanente Medical Group, 10350 E. Dakota Avenue, Denver, Colorado 80231-1314, 303-344-7838 or fax your CV with a cover letter to Physician Recruitment at 303-344-7818.
W-RH1N.792.5X

Massachusetts

Massachusetts, Cambridge. Harvard teaching hospital seeks BC-BE rheumatologist to take over busy, well established practice. Please fax CV to 617-499-5620.
W-RH1N.769.4X

Utah

Rocky Mountains - Multispecialty Clinic. Live; work at the base of the Wasatch Mountains; within 20 minutes of freshwater mountain lakes; trout streams, hiking, biking, camping, hunting. Within 20 minutes of 3 ski areas including 2002 Olympics downhill venue. Located within a few hours of several national parks and monuments. Growing, financially sound 40+ provider, physician-owned and operated multispecialty clinic located within a thriving 85,000+ culturally diverse community. 300,000 + drawing area. Numerous cultural and outdoor recreational activities. Within 35 minutes of progressive city of 200, 000, with professional sports teams, symphony, and ballet. Fax or email CV to Pam Weiss, PHR 801-476-2670 or pweiss@ogden-clinic.com: Phone 801-476-2296.
W-RH2N.123.3X

Rocky Mountains - Multispecialty Clinic. Live, work at the base of the Wasatch Mountains, within 20 minutes of freshwater mountain lakes, trout streams, hiking, biking, camping, hunting. Within 20 minutes of 3 ski areas including 2002 Olympics downhill venue. Located within a few hours of several national parks and monuments. Growing, financially sound 40+ provider, physician-owned and operated multispecialty clinic located within a thriving 85,000+ culturally diverse community. 300,000 + drawing area. Numerous cultural and outdoor recreational activities. Within 35 minutes of progressive city of 200, 000, with professional sports teams, symphony, and ballet. Fax or email CV to Pam Weiss, PHR 801-476-2670 or pweiss@ogden-clinic.com: Phone 801-476-2296.
W-EN2N.124.3X

Northeast

Pharmaceutical/Biotechnology Industry career opportunities for BC-BE Rheumatology Physicians. Send your CV, "in confidence" to Bruce Rogers Company, Management Consultants, 20 Main Street, Port Washington, NY 11050; 800-942-6663; e-mail: BRUROG-CO@aol.com.
W-RH1N.190.24X

Administration

California

Chief of the Division of General Internal Medicine San Francisco Veterans Affairs Medical Center, University of California, San Francisco. The University of California, San Francisco (UCSF) is searching for a Chief of the Division of General Internal Medicine at the San Francisco Veterans Affairs Medical Center (SFVAMC). This will be at the professor or associate professor rank in the In Residence or Clinical medicine academic series depending on qualifications. The Division of General Internal Medicine at the SFVAMC is an active component of the UCSF general internal medicine group and deeply involved in care and teaching, and conducts an aggressive research portfolio particularly focused on outcomes of medical intervention and disease prevention. The successful candidate will be a recognized leader in academic general internal medicine with a focus either in innovative educational approaches or inpatient oriented research. The division is responsible for coordinating outpatient medical care in internal medicine and in providing inpatient medical consultations. The division is the home for a residency program focused on clinical research methodology and has a leading role in directing the UCSF categorical residency training program. The candidate should be Board-certified in internal medicine with additional training in an area appropriate to academic general internal medicine. Send CV to Seth Landefeld, MD, (Search Committee Chair) c/o Jackie Benson, 4150 Clement St., VAMC 181G, San Francisco, CA 94121. UCSF is an affirmative action/equal opportunity employer. The university undertakes affirmative action to assure equal employment opportunity for underutilized minorities and women, for persons with disabilities, and for Vietnam-era veterans and special disabled veterans.
W-AP1N.706.5X

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Administration *continued*

Chief of the Division of Infectious Diseases San Francisco Veterans Affairs Medical Center, University of California, San Francisco. The University of California, San Francisco (UCSF) is searching for a Chief of the Division of Infectious Diseases at the San Francisco Veterans Affairs Medical Center (SFVAMC). This will be at the professor or associate professor rank in the in residence or clinical medicine academic series, depending on qualifications. The Infectious Disease Program of the SFVAMC is fully integrated with the infectious disease division of UCSF, and is an active training site for UCSF infectious disease fellows. The division has a mission including excellence in patient care, teaching, and research, and the successful candidate will be skilled in managing this balance. He or she will be a recognized leader in the field of infectious diseases. A focus on HIV infection is preferred, as is a background in research linking laboratory and patient-oriented investigators. The SFVAMC is a key component of the UCSF-GIVI center for AIDS research and the division chief will be invited to interact with that center. In addition, the SFVAMC is focused on research in hepatitis viruses, particularly HCV. Candidates should be Board-certified in internal medicine and infectious disease. Send CV to Paul A. Volberding, MD, (Search Committee Chair) c/o Paige Cooke, 4150 Clement St., VAMC 111, San Francisco, CA 94121. UCSF is an affirmative action/equal opportunity employer. The university undertakes affirmative action to assure equal employment opportunity for underutilized minorities and women, for persons with disabilities, and for Vietnam-era veterans and special disabled veterans.
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Chief of the Division of Hematology/Oncology San Francisco Veterans Affairs Medical Center University of California, San Francisco. The University of California, San Francisco (UCSF) is searching for a Chief of the Division of Hematology/Oncology at the San Francisco Veterans Affairs Medical Center (SFVAMC). This will be at the professor or associate professor rank in the in residence or clinical medicine academic series, depending on qualifications. The successful applicant will have an active academic background in either or both hematology and oncology, and will be able to lead a division with a mission of excellent patient care, teaching, and research. As an integrated program with the UCSF Cancer Center, the applicant should have a research portfolio complementary to the center and appropriate to the patient population served within the VA system. A focus on research that combines basic and clinical investigation is desirable but not essential. The division participates in the UCSF Hematology/Oncology fellowship training program. Candidates should be Board-certified in internal medicine and either hematology or oncology. Send CV to David Wofsy, MD, (Search Committee Chair) c/o Paige Cooke, 4150 Clement St., VAMC 111, San Francisco, CA 94121. UCSF is an affirmative action/equal opportunity employer. The university undertakes affirmative action to assure equal employment opportunity for underutilized minorities and women, for persons with disabilities, and for Vietnam-era veterans and special disabled veterans.
W-AP1N.707.1X

Texas

Assistant/Associate Professor. The University of Texas Medical Branch, Department of internal medicine, general medicine division in Galveston, TX is seeking qualified candidates for an academic position directing the private practice group. Applicants with an interest/experience in health outcomes research are preferred. Position includes a competitive salary and excellent benefits. Candidates will be joining a vibrant, thriving division of clinician-educators and hospitalists. Applicants should be B/C or B/E in internal medicine and meet TX state licensure requirements with specific interest in medical education. Interested candidates should send CV to: Alice J. Speer, M.D., Director, General Internal Medicine, Department of Internal Medicine, UTMB, 4.174 JSA (Rt. 0566), Galveston, TX 77555-0566; E-mail: aspeer@utmb.edu; Fax: 409-772-4182. UTMB is an equal opportunity employer, M/F/D/V. Minorities and females are encouraged to apply. UTMB only hires individuals authorized to work in US.
W-AP2N.118.1X

ANNALS

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Multiple Specialties/ Group Practice

Texas

Austin, TX: The Austin Diagnostic Clinic is a 120-physician, multispecialty group located in the heart of the Hill Country. Owned and operated by the physicians, salaried positions are available, with partnership potential after 2 years. Position include competitive compensation and complete benefits package. We currently see BC-BE physicians in the following specialty areas: Dermatology, Endocrinology, Hematology/Oncology, Internal Medicine specialists (office based and hospitalists), Neurology, Pulmonary/Critical Care, Radiology, General Surgery and Urology. For immediate consideration, Fax CV to 512-901-3994 or e-mail: repenstein@adclinic.com. Or contact Raquel "Rocky" Epstein at 1-800-203-2710 from 8:00 am-5:00 pm, CST. Sorry, no J1 Visa Waiver opportunities in our area. www.adclinic.com.
W-MG2N.125.8X

Residencies and Fellowships

Illinois

Abbott Laboratories Physician Training Program. In Pharmaceutical Drug Development. A unique training opportunity for physicians who have completed a residence program with a career interest in joining a pharmaceutical company. Two year training position including drug safety reporting. Clinical pharmacology, outcomes research and clinical development - Phase I-IV. For application and additional information contact: Anthony Japour, M.D., Abbott Laboratories, D-4NF/AP30-3, 200 Abbott Park Road, Abbott Park, IL 60064-6145, or Jackie Harmann, Clinical Administrative Specialist, jackie.harmann@abbott.com.
W-RF1N.744.4X

Pennsylvania

Residency Position, Internal Medicine. Second-year position available July, 2002 at York Hospital, a 588-bed community teaching hospital in south-central Pennsylvania, affiliated with Pennsylvania State University, University of Maryland and University of Pennsylvania. Excellent teaching provided by large full-time/voluntary staff. Educational program designed to prepare physicians for practice of general internal medicine or further subspecialty training. Contact: Wolfe Blotzer, M.D., Program Director, Department of Medicine, York Hospital, 1001 S. George Street, York, PA 17405. Telephone 717-851-2164.
RF1N.725.5X

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Henry Ford
HEALTH SYSTEM

DIVISION HEAD
INFECTIOUS DISEASE

The Henry Ford Health System is seeking a Division Head for Infectious Disease in the Department of Medicine. This is one of the nation's leading comprehensive health systems, providing acute, primary and preventive care services.

The Division has 8 physicians providing inpatient and outpatient services throughout southeastern Michigan, 4 fellowship participants and a nationally recognized basic and clinical research. The Division Head reports to the Department Chair and is expected to advance the division's clinical, education and research mission both on a department and system-wide basis. A collaborative leadership style, strong academic credentials and a proven track record in administration and finances is required.

Board certification in both Internal Medicine and Infectious Disease is required.

Send curriculum vitae to: Dr. John Popovich, Chair, Department of Medicine, 2799 W. Grand Blvd., Detroit, MI 48202 or fax c.v. to (313) 916-1394. AA/EEO

CD1.281.2x

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The Cleveland Clinic's newest medical center in Naples, Florida is seeking a highly qualified Board Certified/Eligible candidate for:

Director of
INTERNAL MEDICINE

Naples offers an ideal climate with high patient demand in a rapidly growing community. The Cleveland Clinic in Naples is a state-of-the-art facility growing to meet this demand. If you are searching for a unique opportunity to be a part of our expansion into Southwest Florida send your C.V. to:

Cleveland Clinic Florida
Attn: Office of Professional Staff Affairs;
2950 Cleveland Clinic Blvd., Weston, FL 33331:
Fax (954)659-6012

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CLEVELAND CLINIC
FLORIDA

CD2.101.6x

Southwest Medical Associates is Nevada's largest multispecialty group. We are expanding our inpatient department to accommodate for the growth in the area. We are looking for board certified internists with at least two years experience. Schedule : 12 hour shifts / 7 days on and 7 days off. Generous benefit package, Compensation (DOE). NV has no state income tax. Paid vacation, CME days/dollars, sick/personal time and holiday. Medical/dental/vision, professional liability, relocation and much more. No J-1 or H-1b Visas.

Please fax your CV to
Kristin Grimes at 702-258-3628
or email CV to
kristinw@sierrahealth.com

CD2.107.3x

INTERNAL MEDICINE

Several immediate opportunities available for BC/BE Internists to join established medical practices in **southern New Hampshire**. Elliot Health System located in Manchester, NH – 46 miles NW of Boston, is seeking physicians with strong work ethic and commitment to quality care. To inquire, please fax CV with cover letter to:
Maureen Mulligan, 603-663-4999
or email mmulligan1@Elliot-hs.org

CD1.405.1x

Internist

GVH, a member of Main Line Health is currently seeking a part-time (with potential for full-time) Internist interested in Geriatric medicine. Our practice combines outpatient, CCRC, and hospital patients in the Philadelphia area. Please forward resume to Attn: LM, Paoli Pointe Building, 11 Industrial Boulevard, Paoli, PA 19301. Fax: (610) 296-2837 or email marinakosl@mlhs.org. EOE.

Main Line Health
Great Valley Health
Jefferson Health System

CD2.102.1x

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Clinically excellent, congenial internal medicine department seeking new members for our team. Diverse, challenging practice in state-of-the-art clinic and hospital facilities. Friendly community, good schools, and fabulous outdoor activities-hike, bike, fish, ski, kayak.

For more information contact
Rochelle Woods 800-303-6893
or rdwoodsmmg@aol.com

CD2.111.1x

INTERNAL MEDICINE/ENDOCRINOLOGIST
SOUTHERN CALIFORNIA

Alvarado Hospital Medical Center is seeking an internal medicine/endocrinology specialist to join a well-established two-man practice which is in the process of expanding. This is a unique and excellent professional opportunity. A solid core competency in endocrinology combined with dedication to the highest standards of teamwork and best possible outcomes define the ideal candidate. A relocation package is included.

Alvarado Hospital, located in San Diego, California has 281 acute beds and is a full service community based hospital complete with the most advanced diagnostic and therapeutic technology.

The Candidate should be Board Certified/Board Eligible. Relocation package commensurate with the candidate's qualifications. Please send Curriculum Vitae to:

Diane Fore, Associate Administrator
Alvarado Hospital Medical Center
6655 Alvarado Road *San Diego, Ca 92120-5298
Phone 619-229-3249 * Fax 619-287-0909
Email: diane.fore@tenethealth.com

Alvarado
Hospital Medical Center

CD1.436.3x

INTERNAL MEDICINE
SOUTHWEST MISSOURI

Freeman Health System

Quality medicine in the 21^{st} Century. Three BC Internal Medicine physicians are overbooked and overworked. They need you to join their group. One in four call, state of the art equipment, all specialties represented, share office space. Excellent facilities: The Freeman Heart Institute, Freeman Cancer Institute and a new forty bed ICU opening in 2002. South-west Missouri can offer your family recreational activities, excellent private & public schools, low cost of living & low crime rate, mild climate. **Most of all a great place to call home!**

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or fax to 417-347-9320
or email: njpaul@freemanhealth.com

CD2.104.3x

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Incorporated

ARIZONA HOSPITALIST OPPORTUNITIES

American Physicians, Inc. (API), is a multi-specialty physician group that has experienced tremendous growth by putting the patient and physician first. Our mission is to provide a unique, efficient and cost effective framework in which a doctor can concentrate on caring for his or her patients and earn a competitive wage.

Our practice has opportunities for full-time hospitalists in Phoenix and Tucson. Candidates must possess outstanding clinical and interpersonal skills. Physicians with our group enjoy excellent compensation and full company benefits.

No J1/H1 Visa opportunities.

Please submit CV or questions to: Vicky Rinehart, Director of Business Development
2020 North Central Avenue, Suite 1200
Phoenix, AZ 85004
Phone (602)553-8400
Fax (602)553-8408
Email vrinehart@americanphysicians.net

CD1.417.3x

SPRINGFIELD, MISSOURI
Internal Medicine Positions

Join the Internal Medicine Department at St John's Health System, Springfield, Missouri. Admit to St. John's Regional Health Center, an 886-bed tertiary center that provides care to a population of more than one million people. Positions offer guaranteed salaries and full benefit packages, including health, life, disability, retirement, vacation, malpractice, relocation, and CME. **Not a J-1 eligible position.**

SPRINGFIELD, MISSOURI, is a sophisticated, yet congenial, medical community. This growing mid-sized city in the foothills of the Ozark Mountains offers everything from Broadway performances and minor league and Division I athletics to outstanding schools and some of the best outdoor sporting opportunities available in the Midwest. In 2001, *Employment Review* named Springfield one of the 20 "Best Places to Live and Work" in the U.S. Housing costs, projected job growth, education, healthcare, taxes, recreation, the arts, and general cost of living rates, make living and working here a pleasure. For more information about Springfield, go to www.springfield.missouri.org.

Carol Murrow, Physician Recruiter
St. John's Health System
1965 S Fremont, Suite 3950
Springfield, MO. 65804
Phone: 877-880-6650
Fax: 888-290-8300
E-mail: cmurrow@sprg.smhs.com

CD1.360.3x

Covenant
Medical Group

Internal Medicine
Big Spring, Texas and Hobbs, New Mexico

Covenant Medical Group (CMG), an affiliate of Covenant Health System is seeking two BE/BC internists with excellent clinical, technical and interpersonal skills for traditional IM practices. Position in Hobbs, New Mexico will join an established 8 physician multi-specialty group and a second position is available to join a 15 physician multi-specialty group in Big Spring, Texas.

CMG is a multi-specialty group of more than 220 physicians across West Texas and Eastern New Mexico delivering healthcare to 1.5 million lives. We offer a competitive salary and an excellent benefit package that includes medical/dental insurance, life insurance, vacation/holidays, 403(b), reimbursements for CME and other benefits. CV should include salary requirements and can be forwarded to Covenant Medical Group

Attn: Kelly Reeves
6502 Slide Rd., Suite 205, Lubbock, TX 79424
or faxed to 806-725-9820.
For telephone inquiries call 806-725-9975.
www.covmedgroup.org

CD2.106.6x

SOUTHEAST PRACTICE OPPORTUNITIES
Hospitalist and Traditional practices throughout the southeast. All searches confidential.
Contact **MED-PRO**
At 800-544-5510 Fax: 910-256-6961
PO Box 837, Wrightsville Beach, NC 28480
E-mail medpro@medpro-search.com
www.medpro-search.com

CD2.105.6x

HOSPITAL-BASED INTERNIST

The Everett Clinic, a 190+ physician, rapidly growing physician-owned and managed multispecialty group, is seeking BC/BE experienced Hospitalist to join established, expanding team. Successful candidate must have additional training in Critical Care or significant ICU experience. Weekdays 7-5, critical care call evenings/weekends 1:6. Available now. Opportunity for exceptional personal/professional lifestyle in Seattle Metro area. Competitive salary with excellent benefits. See our website for more information: www.everettclinic.com Send CV and cover letter to: Libby Atkinson The Everett Clinic, 3901 Hoyt Avenue, Everett, WA 98201 or fax to 425-339-5405.

CD2.103.3x

MeritCare **HOSPITALIST**
North Dakota

MeritCare Health System is seeking a third BC/BE internist to provide care to hospital patients. Candidate will join a diverse 26-member department and work with the University of North Dakota School of Medicine Internal Medicine Residency Program. MeritCare is an integrated 335-physician multi-specialty group practice and 380-bed tertiary/trauma hospital. Sister cities, Fargo, ND and Moorhead, MN, were recently named an 'All American City'. A tri-college community of 166,500 people. Fargo-Moorhead is located on the southeastern border of North Dakota, just a few miles from the lake country of western Minnesota. Recreational and sporting activities abound, and as the area's largest city, Fargo-Moorhead serves as the regional cultural center. This is an excellent practice opportunity with a competitive compensation and benefits package being offered. EOE/AA. This is not a HPSA designated site. No J-1 visa waivers available. To learn more about this practice opportunity contact:

James Volk M.D.
at (800) 437-4010, ext. 2261,
or email your CV to
jillgilleshammer@meritcare.com
or via fax to (701) 234-2316

CD1.413.3x

University of Pennsylvania

The Department of Medicine/Division of General Internal Medicine at the University of Pennsylvania's School of Medicine seeks candidates for Assistant, Associate and/or Full Professor positions in the non-tenure clinician-educator track. Rank will be commensurate with experience. Applicants must have an M.D. degree and be Board Certified or Board Eligible. Positions are available for Hospitalists dedicated to in-patient teaching service.

The Division also is seeking candidates for Assistant, Associate and/or Full Professor positions in the tenure and non-tenure research tracks. Rank and Track will be commensurate with experience and career goals. Expertise in Health Services Research is required. Applicants must have an M.D. or M.D./PhD. degree, and have demonstrated excellent qualifications in research. We are seeking candidates with plans for an independent research program and a record that demonstrates knowledge, skill and the ability to conduct research.

Please submit curriculum vitae, letter of interest, and 3 reference letters to:

Sankey Williams, M.D., Chief, General Internal Medicine, 423 Guardian Dr., 12th flr., Blockley Hall/6021, Phila, PA 19104

Affirmative Action / Equal Opportunity Employer

CD2.116.1x

Boise, Idaho!

Saint Alphonsus Regional Medical Center is looking for 2 **Hospitalists** to start a new program. We are looking for someone who is Board Certified with excellent clinical and communication skills. Experience as a Hospitalist required.

About Saint Alphonsus

- State-of-the-art 281 bed Regional Medical and Surgical Center
- Advanced surgical specialties of General, Vascular, Orthopaedic, Neurological and Cardiac Medicine
- Comprehensive Cancer Treatment Center
- Regionally acclaimed Diagnostic Radiology services
- Regional Level II Trauma Center Service area population of 500,000

This position offers very competitive salary and benefits. For more information about this exceptional opportunity contact: Beth Vance-Wehrli at 1-800-309-5388, fax CV to 208-367-7964 or e-mail bethvanc@sarmc.org

This position does not qualify for J1 visa wavier applicants.

CD2.117.3x

The Medical Opportunity Of A Lifetime On Florida's Gulf Coast

Life's too short to practice medicine just anywhere. An inviting career opportunity awaits you with Morton Plant Mease Primary Care, a dynamic, multi-hospital Florida health care organization with an exciting future.

Room to Grow for Quality Physicians

(BE/BC only) For summer, 2002. J1 Visa not eligible. Continued growth is creating exciting opportunities in Family Practice, Internal Medicine, Hospitalist and Urgent Care for practicing physicians and graduating residents.

Start living the medical career of your dreams. Fax your CV to Kathy Sadler, Manager of Physician Relations, (727) 536-5903 or email to Kathy.Sadler@baycare.org.

To learn more about rewarding physician opportunities, call 1-800-875-8254. www.mpmhealth.com and www.mpmprimarycare.com

Morton Plant Mease
PRIMARY CARE

CD2.108.3x

INTERNAL MEDICINE

General Internal Medicine physician to join a well-established multi-specialty group. Practice within this professional environment offers strong collegial support and favorable call schedule 1:9. We have our own state-of-the-art in-house ambulatory day surgery unit. Our service area is a 3-county region serving a population of 90,000 located on the southern Oregon coast. NBMC is a 40-physician group with three satellite clinics.

Safe family oriented community offers rewarding lifestyle with excellent school system, and many recreational activities on the beautiful Oregon coast.

Please send CV to Marce Knight

NBMC
MEDICAL CENTERS
Coos Bay · Coquille · Gold Beach · Brookings · Bandon

1900 Woodland Drive
Coos Bay, Oregon 97420;
1-800-765-0052 x294, fax 541-267-0500
or e-mail at marcekight@nbmc.com

CD2.110.3x

INTERNIST

BC-BE to join 10 member IM department in well established multispecialty group practice in northern CA. Practice is a mix of ambulatory and inpatient care, with hospital adjacent to clinic. Competitive salary and reasonable call. Excellent schools and affordable housing in close proximity to Lake Tahoe, wine country, and San Francisco.

Send CV to:
P. Laughlin, MD, at
1325 Cottonwood Street
Woodland, CA 95695-4398
or Fax: 530-666-7948 or
Email plaughlin@chw.edu

CD2.115.3x

Academic General Internist

Dynamic, University-affiliated, community based internal medicine residency seeks physician for full time faculty position. Inpatient-Outpatient teaching, direct patient care, program development. Small program with unique ambulatory training model with resident mentorship. EMR with strong ability for outcomes research. Stable faculty and leadership. Positive work environment. If you seek professional satisfaction in the beautiful Northwest please send your CV to

Robert Gluckman, M.D., FACP, Medical Director
Dept. of Medicine Faculty Practice
Providence St. Vincent Medical Center
9205 SW Barnes Road, MT-2800
Portland, OR 97225
Fax (503) 216-7488
email: rgluckman@providence.org
www.providence/oregon.org

Providence | Health System

CD1.380.1x

Group practice position available for BC/BE internist on the **beautiful central Oregon coast**. Full spectrum internal medicine with an excellent 50-bed community hospital. Central Coast Internal Medicine is a well established group of 3 physicians and 2 PAs. No J-1 opportunities.

Contact CCIM
775 SW 9th, Suite B,
Newport, OR 97365
e-mail to CentralCoastIM@yahoo.com

CD1.407.6x

INTERNAL MEDICINE

Exceptional opportunity for Board certified/eligible, internal medicine physician to join our team of three providing medical care to patients in a rural community of 100,000. Candidate should be able to obtain a SC license. Excellent benefits and income guarantee.

TUOMEY
HEALTHCARE SYSTEM

Address inquiries and CV to:
Professional Recruitment
Tuomey Healthcare System
129 N. Washington St., Sumter, SC 29150
or e-mail same to luebbert@tuomey.com

CD2.112.3x

FLORIDA-PENSACOLA
HOSPITALIST/INTERNAL MEDICINE

Innovative Ohio based hospitalist company is pleased to announce our expansion to Florida and our affiliation with the Sacred Heart Health System. Hospitalist positions will be available in Spring 2002 with this highly regarded 431-bed acute care hospital system. Outstanding professional setting includes established business/support resources and directorship by a pioneer in the field. Our growth will provide for career development through expansion and administrative options. Enjoy an excellent compensation package including partnership/profit sharing. Fully funded pension, flex savings plan, 401(k), professional liability coverage, CME account, health/ dental/ life disability insurance and more.

Contact Jim Nicholas (careers@emp.com)
Hospitalists Management Group, Ltd
A division of Emergency Medicine Physicians, Ltd.
4535 Dressler Road NW, Canton, OH 44718
(800) 828-0898 or fax CV to (330) 493-8677

CD2.118.1x

MAINE. Our thriving inpatient medicine program has recently welcomed excellent internists from New York City, Massachusetts and Florida. Join a collegial team of eight physicians and two mid-level providers, utilizing a block shift model with no call. The addition of a teaching service and a palliative care program will require additional BC/BE internists who enjoy inpatient medicine, including the care of critically ill patients, and who are motivated by a unique opportunity to experience the way life and medicine should be. Our regional referral center provides state of the art specialty care for a third of Maine's population. The area offers safe, healthy and affordable living. Schools are ranked among the best in New England, earning distinction for test scores, music, art and sports; and the University of Maine's flagship campus is minutes away. A vibrant arts calendar features a community orchestra, youth symphony, repertory theater, and performing artists from around the world. We enjoy easy access to the coast, mountains and lakes that offer exceptional hiking and cycling, sailing and kayaking, skiing, hunting and fishing. Not a J1 opportunity.

To send CV or request more information contact:
Ann Trainor, Physician Liaison
EASTERN MAINE HEALTHCARE
489 State St., Bangor
Maine 04401
Phone 207-973-7444
Fax 207-973-4977

CD1.308.3x

Internal Medicine Opportunities

St. Mary's/Duluth Clinic Health System is seeking Internal Medicine Physicians for clinics in Duluth, MN, Ashland, WI, Superior, WI and Virginia, MN. (Not a J-1 waiver opportunity)

SMDC is a 350 + physician multi-specialty clinic with more than 20 clinic Locations and four hospitals, serving a referral populations of 460,000 in northeastern Minnesota, northwestern Wisconsin, and upper peninsula of Michigan. SMDC has been awarded three Top 100 awards during the past year: SMDC Regional Heart Center: Top Cardiovascular Intervention Program, Top 100 Orthopedic Fracture Repair Program, St. Mary's Medical Center and Top 100 Hospital. SMDC is the largest most comprehensive provider of primary, secondary and tertiary health care services in the region.

Fax or mail your CV to:

Cathy Ziegler Physician & Provider Recruitment
St.Mary's/Duluth Clinic Health System
400 E. 3rd St., Drop SHL 40 Duluth MN. 55805
1-800-342-1388 ext. 63293, 218-786-3293
fax: 218-722-9952 e-mail: cziegler@smdc.org
Websites: www.smdc.org or www.duluth.com

SMDC
St. Mary's/Duluth Clinic
Health System

CD2.119.3x

Director,
Center for Health Economics and Modeling

Provide scientific leadership and operational management for a growing scientific staff. Required graduate-level health services research and economics training with M.D. or Ph.D.. Must have management experience in a contract research environment and a strong record in medical technology assessment, health economics, or health services research as demonstrated by publication in peer-reviewed journals.

MEDTAP International, a world leader in health economics and outcomes research, is headquartered in Bethesda, Maryland with offices in Seattle, London and Amsterdam. MEDTAP scientists perform challenging work in a stimulating, collegial environment. MEDTAP offers an excellent compensation package, including a comprehensive health insurance program, a 401-K retirement plan and participation in an equity stock plan. MEDTAP is an EOE/AA employer.

For confidential consideration, please provide your curriculum vitae, copies of recent publications, and salary requirements to:

Bryan R. Luce, Ph.D., MBA
President & CEO
MEDTAP International, Inc.
Suite 600
7101 Wisconsin Avenue
Bethesda, MD 20814.
e-mail ***luce@medtap.com***

MEDTAP
International

CD1.440.1x

ST. JOHN'S
HEALTH SYSTEM

HOSPITALISTS

St. John's Health System in Springfield, Missouri, seeks 2 hospitalists to join 6 IM Board Certified Hospitalists. Manage patients from admit to discharge, floor to ICU and back, and participate in system-wide quality improvement projects. Positions offer competitive salaries, bonus potential, and include a full array of benefits including health, dental, vision, life and disability insurance, malpractice, CME, vacation, retirement, and relocation.

St. John's Regional Health Center is an 886-bed facility that provides care to a service area of more than one million people. Our Level I Trauma designation makes St. John's a regional referral center for southwest Missouri and northwest Arkansas. **Not a J-1 eligible position.**

SPRINGFIELD, MISSOURI, is a sophisticated, yet congenial, medical community. In 2001, *Employment Review* named Springfield one of the 20 "Best Places to Live and Work" in the U.S. Housing costs, projected job growth, education, healthcare, taxes, recreation, the arts, and general cost of living rates, make living and working here a pleasure. For more information about Springfield, go to www.springfield.missouri.org.

Carol Murrow, Physician Recruiter
St. John's Health System
1965 S. Fremont, Suite 3950, Springfield, MO. 65804
Phone: 877-880-6650 Fax: 888-290-8300
E-mail: cmurrow@sprg.smhs.com

CD1.385.1x

MAYO CLINIC SCOTTSDALE

Chair, Division of Regional and International Medicine

Mayo Clinic Scottsdale, a 260-physician academic, multi-specialty group practice located in Scottsdale, Arizona, seeks an outstanding clinician committed to high quality patient care, research and education in a tertiary care, primarily outpatient setting.

The Division of Regional and International Medicine is an ambulatory, outpatient practice providing consultative general medical care to patients living outside of the Maricopa County region. Patients seen come from all over the United States, as well as international locations. The Division is not intended to practice primary care or inpatient internal medicine.

The successful candidate will serve as a mentor to junior faculty, encourage clinical practice, research and education and have the opportunity to lead a growing consultative general internal medicine practice. Applicant will also be expected to set the direction of the Division, lead by example, develop consensus building, and fulfill the expectations of the Division, the Department of Medicine, and the Mayo Clinic Scottsdale Board of Governors.

Candidates must be board certified in Internal Medicine, with an additional year of training in advanced General Internal Medicine desirable. Five years of clinical practice experience required with three years of leadership experience in an academic medical center preferred. Candidates should also have outstanding leadership and administrative skills and possess demonstrated excellence in research and education. Diversity in language skills desirable.

Mayo Clinic offers competitive compensation and comprehensive benefits, including a relocation package. For consideration, please forward a letter of intent and curriculum vitae to: **Pasquale J. Palumbo, M.D., Chair, Department of Internal Medicine, Mayo Clinic Scottsdale, 13400 E. Shea Boulevard, Scottsdale, AZ 85259,** or email: **palumbo.pasquale@mayo.edu**

As an equal opportunity employer, we value diversity.

For additional employment opportunities, visit our website at: www.mayo.edu

mayo

CD2.209.1x

PRESBYTERIAN HEALTHCARE SERVICES
NEW MEXICO

INTERNAL MEDICINE PHYSICIANS

New Mexico will enchant you with an easy-paced lifestyle, diverse culture, year-round recreational activities and sunshine. Presbyterian Healthcare Services (PHS) is the state's largest private non-profit hospital system with hospitals and clinics throughout New Mexico. We have opportunities for BE/BC internal medicine physicians in primary care clinics **OR** as hospitalists in the following locations:

- Albuquerque, NM (openings in outpatient clinic **OR** join our hospital inpatient team)
- Ruidoso, NM (resort area in So. Central NM) full time clinic opening

These opportunities offer a competitive salary; paid malpractice, relocation, CME allowance, pension, 403 (b), health, life, AD&D disability insurance, dental, vision pretax health and child care spending accounts. (not J-1, H-1 opportunities). For more information, please contact: Kay Kernaghan, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125; 800-545-4030, ext. 8593; Fax: (505) 923-8759 or e-mail KKernagh@PHS.org.

PRESBYTERIAN
Healthcare Services

CD2.114.3x

Fellowships in Critical Care Medicine, Critical Care/Pulmonary, or Critical Care/Infectious Diseases

The Warren G. Magnuson Clinical Center of the National Institutes of Health (NIH) is a unique clinical research environment that bridges basic science and direct patient care. The Critical Care Medicine Department serves all the Institutes at NIH , providing a unequalled opportunity for collaboration with some of the most highly regarded physicians and researchers in the world. The senior staff of the Department consists of ten physicians with subspecialty training in pulmonary, cardiology, anesthesiology, infectious diseases, and critical care; all are involved in active research programs.

Opportunities for ACGME-accredited fellowships are available beginning **July 2003.** The first year consists of clinical training in the intensive care units at the NIH, at a large regional surgery and trauma center, and at other university-affiliated hospitals. These rotations provide broad experiences in the management of critically ill patients, while developing a variety of procedural skills. The second and elective, additional years consist of individually-designed programs in clinical or basic research related to critical illnesses. Eligible fellows may combine training in critical care medicine with training in infectious diseases or pulmonary medicine. **Student Loan Repayment of $5,000 to $35,000 per year is available to qualified individuals accepted into the program.**

Fellows must have completed a residency in either internal medicine or anesthesiology. Physicians with additional advanced training, particularly in infectious diseases or pulmonary medicine, are also encouraged to apply. **Applications for July 2003 positions will be accepted until March 31, 2002.** Applications consist of a curriculum vitae and three letters of recommendation and should be sent to Frederick P. Ognibene, MD, FACP, FCCM, Fellowship Program Director at the address listed below.

National Institutes of Health

Critical Care Medicine Department
10 Center Drive Building 10, Room 7D43 Bethesda, MD 20892-1662
Phone: 301-496-9320 FAX: 301-402-1213 Email : ccmprogram@mail.cc.nih.gov
http://www.training.nih.gov/clinical/physician/asp/index.asp

NATIONAL INSTITUTES OF HEALTH

NIH is an equal opportunity employer and invites applications for all qualified individuals

CD1.409.6x

Ochsner
CLINIC

INTERNAL MEDICINE PHYSICIANS

Ochsner Clinic Foundation New Orleans has outstanding opportunities for Board Certified/Board Eligible Internal Medicine Physicians who would like to practice in a large multi-specialty group practice.

Ochsner Clinic is an integrated health care system with over 400 physicians in over 25 locations across Southeast Louisiana. Ochsner has its own HMO, outstanding post-graduate education programs, and research opportunities.

We offer competitive salaries and attractive benefits. New Orleans and surrounding areas offer numerous cultural, historical, and recreational activities.

SORRY, NO J-1 VISA OPPORTUNITIES

Please send curriculum vitae to:

Ochsner Clinic Foundation, Ref# AGIMNO
P.O. Box 82109
Baton Rouge, Louisiana 70884-2109
Info: (800) 488-2240, Fax: (225) 761-5441 or
E-mail: isumly@ochsner.org

CD[illegible].362.3x

Hospitalist

BE/BC Internist to join established program serving 285 bed regional referral and teaching hospital with 200,000 patient population referral base. Easy access to Minneapolis, Minnesota and Des Moines, Iowa. Family oriented community of 30,000 people. Comprehensive benefits and competitive compensation.

Contact: Jerry Hess
Mercy Medical Center – North Iowa
1000 4th Street S.W.
Mason City, IA 50401
hessj@mercyhealth.com
888-877-5551 Fax: 641-422-6495

CD2.113.3x

NEPHROLOGIST BC/BE

Los Angeles, California—University affiliated, prestigious multispecialty group seeks BC/BE nephrologist to join busy existing practice – dialysis, CAPD, transplants. Competitive salary and benefits, with full-time employment leading to shareholder eligibility in two years. Great opportunity, supportive peers and strong medical leadership.

Please fax your CV to 310-659-3508
or call 310-659-4320.

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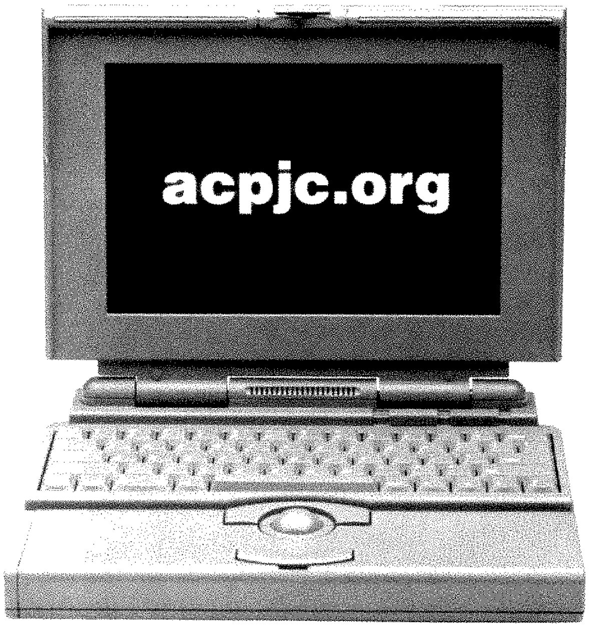
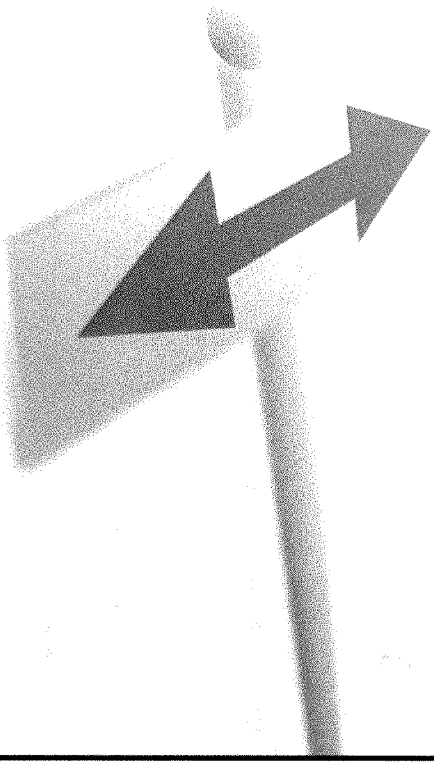


Resources for Career Choices

go to: www.acponline.org/careers

Visit the ACP–ASIM Online Career Resource Center



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Why would you search anywhere else?

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American College of Physicians

American Society of Internal Medicine

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FILA

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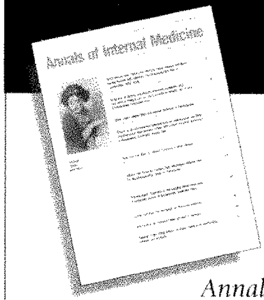
*Demographic Edition

While every precaution is taken to insure accuracy, we cannot guarantee against an occasional change or omission in the preparation of this index.

Keep up with *important* information



Annals of Internal Medicine

Annals of Internal Medicine is the in-depth clinical journal for practicing physicians in internal medicine and its subspecialties. *Annals* is renowned for its clear, accurate, and rigorous analysis and perspective.

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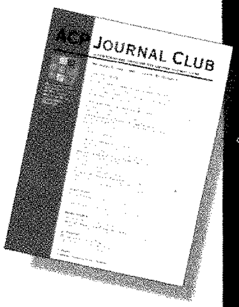
ACP Journal Club



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ACP ASIM

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Fax: 215-351-2799,

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Online ordering is now available.

CELEBREX®
(celecoxib capsules)

Brief summary of prescribing information.

INDICATIONS AND USAGE
For relief of the signs and symptoms of osteoarthritis (OA), and of rheumatoid arthritis (RA) in adults. For the management of acute pain in adults. For the treatment of primary dysmenorrhea.

CONTRAINDICATIONS
CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib. CELEBREX should not be given to patients who have demonstrated allergic-type reactions to sulfonamides or to those who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS — Anaphylactoid Reactions, and PRECAUTIONS — Preexisting Asthma).

WARNINGS
Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation: Serious GI toxicity (bleeding, ulceration, and perforation of the stomach, small intestine or large intestine) can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Inform patients about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, occur in about 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. It is presently unclear how the above rates apply to CELEBREX . Among 5,285 patients who received CELEBREX in controlled clinical trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 200 mg or more, 2 (0.04%) experienced significant upper GI bleeding, at 14 and 22 days after initiation of dosing. About 40% of these 5,285 patients were in studies that required them to be free of ulcers by endoscopy at study entry. Thus it is unclear if this study population is representative of the general population. Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking CELEBREX vs. comparator NSAID products have not been performed. Prescribe NSAIDs with extreme caution in patients with a prior history of ulcer disease or GI bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore take special care in treating this population. **To minimize the potential risk for an adverse GI event, use the lowest effective dose for the shortest possible duration.** For high risk patients, consider alternate therapies that do not involve NSAIDs. Studies have shown that patients with a *prior history of peptic ulcer disease and/or GI bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. Pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX. In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS — Preexisting Asthma). Seek emergency help in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease: Treatment with CELEBREX is not recommended, but if it is used, monitoring of kidney function is advised.

Pregnancy: Avoid CELEBREX in late pregnancy because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS
General: CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Hepatic Effects: Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (about three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These lab abnormalities may or may not change with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including CELEBREX. In controlled clinical trials of CELEBREX, the incidence of borderline elevations of liver tests was 6% for CELEBREX and 5% for placebo, and about 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX. Discontinue CELEBREX if clinical signs and symptoms of liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash).

Renal Effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, or liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs. Use caution when initiating treatment with CELEBREX in patients with considerable dehydration. Rehydrate patients first and then start therapy with CELEBREX. Use caution in patients with pre-existing kidney disease (see WARNINGS — Advanced Renal Disease).

Hematological Effects: In controlled clinical trials the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages.

Fluid Retention and Edema: Fluid retention and edema have been reported. Use CELEBREX with caution in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma: Do not use in patients with aspirin-sensitive asthma because of the risk of severe bronchospasm. Use with caution in patients with preexisting asthma.

Information for Patients: Inform patients of the following: GI bleeding which may result in hospitalization and fatal outcomes; to be alert for signs and symptoms of ulcerations and bleeding, and seek medical advice should these be observed; to promptly report GI ulceration or bleeding, skin rash, unexplained weight gain, or edema; to stop therapy and seek immediate medical help if they experience warning signs and symptoms of hepatotoxicity; to seek immediate emergency help in the case of an anaphylactoid reaction; and to avoid CELEBREX in late pregnancy.

Laboratory Tests: Because serious GI tract ulcerations and bleeding can occur without warning symptoms, monitor for signs or symptoms of GI bleeding. During controlled clinical trials, there was an increased incidence of hyperchloremia and other lab abnormalities including hypophosphatemia and elevated BUN in patients receiving celecoxib compared with patients on placebo. These lab abnormalities were also seen in patients who received comparator NSAIDs in these studies.

Drug Interactions: ***General:*** Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by P450 2D6. ***ACE-inhibitors:*** Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. ***Furosemide:*** Clinical studies, and post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. ***Aspirin:*** CELEBREX can be used with low dose aspirin; however, concomitant administration may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX alone. CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis. ***Fluconazole:*** Concomitant administration of fluconazole 200 mg QD resulted in a two-fold increase in celecoxib plasma concentration is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole. Initiate CELEBREX at the lowest recommended dose in patients receiving fluconazole. ***Lithium:*** Mean steady-state lithium plasma levels increased approximately 17% in healthy subjects receiving lithium 450 mg BID with CELEBREX 200 mg BID compared with those receiving lithium alone. Closely monitor patients on lithium when CELEBREX is introduced or withdrawn. ***Methotrexate.*** CELEBREX did not have a significant effect on the pharmacokinetics of methotrexate in rheumatoid arthritis patients. ***Warfarin:*** Monitor anticoagulant activity, particularly in the first few days, after initiating or changing therapy with CELEBREX in patients receiving warfarin or similar agents; these patients are at an increased risk of bleeding complications. In healthy subjects receiving daily doses of 2-5 mg of warfarin, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin. **Carcinogenesis, mutagenesis, impairment of fertility**: Celecoxib was not carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-fold the human exposure as measured by the AUC_{0-24} at 200 mg BID) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24} at 200 mg BID) for two years. Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an in vivo micronucleus test in rat bone marrow. Celecoxib did not impair male and female fertility in rats at oral doses up to 600 mg/kg/day (approximately 11-fold human exposure at 200 mg BID based on the AUC_{0-24}).

Pregnancy: ***Teratogenic effects:*** Pregnancy Category C. Celecoxib at oral doses $\geq$ 150 mg/kg/day (about 2-fold human exposure at 200 mg BID as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses $\geq$ 30 mg/kg/day (about 6-fold human exposure based on the AUC_{0-24} at 200 mg BID) throughout organogenesis. There are no studies in pregnant women. Use CELEBREX during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Nonteratogenic effects:*** Celecoxib produced pre- and post-implantation losses and reduced embryo/fetal survival in rats at oral dosages $\geq$ 50 mg/kg/day (about 6-fold human exposure based on the AUC_{0-24} at 200 mg BID). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are they expected at clinical exposures. No human studies have been conducted on the effect of celecoxib on the closure of the ductus arteriosus. Use of CELEBREX during the third trimester of pregnancy should be avoided. **Labor and delivery**: Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (about 7-fold human exposure as measured by the AUC_{0-24} at 200 mg BID). The effects of CELEBREX on labor and delivery in pregnant women are unknown. **Nursing mothers**: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CELEBREX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**: Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated. **Geriatric Use**: While the incidence of adverse experiences tended to be higher in elderly patients, no substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out

ADVERSE REACTIONS
Adverse events occurring in ≥2% of Celebrex patients from controlled arthritis trials, regardless of causality at recommended doses (N=4146): abdominal pain 4.1%, diarrhea 5.6%, dyspepsia 8.8%, flatulence 2.2%, nausea 3.5%, back pain 2.8%, peripheral edema 2.1%, injury-accidental 2.9%, dizziness 2.0%, headache 15.8%, insomnia 2.3%, pharyngitis 2.3%, rhinitis 2.0%, sinusitis 5.0%, upper respiratory tract infection 8.1%, rash 2.2%. 7.1% of patients receiving CELEBREX and 6.1% for placebo discontinued due to adverse events in placebo or active controlled clinical trials. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (0.8% and 0.7%, respectively). Among placebo patients, 0.6% discontinued due to dyspepsia and 0.6% due to abdominal pain. The following adverse events occurred in 0.1-1.9% of patients regardless of causality.

Celebrex (100-200 mg BID or 200 mg QD): **GI**: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting; ***Cardiovascular:*** Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction; ***General:*** Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain; ***Resistance mechanism disorders:*** Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media; ***Central, peripheral nervous system:*** Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo; ***Female reproductive:*** Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis; ***Male reproductive:*** Prostatic disorder; ***Hearing and vestibular:*** Deafness, ear abnormality, earache, tinnitus; ***Heart rate and rhythm:*** Palpitation, tachycardia; ***Liver and biliary system:*** Hepatic function abnormal, SGOT increased, SGPT increased; ***Metabolic and nutritional:*** BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase; ***Musculoskeletal:*** Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis; ***Platelets (bleeding or clotting):*** Ecchymosis, epistaxis, thrombocythemia; ***Psychiatric:*** Anorexia, anxiety, appetite increased, depression, nervousness, somnolence; ***Hemic:*** Anemia; ***Respiratory:*** Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia; ***Skin and appendages:*** Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria; ***Application site disorders:*** Cellulitis, dermatitis contact, injection site reaction, skin nodule; ***Special senses:*** Taste perversion; ***Urinary system:*** Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection; ***Vision:*** Blurred vision, cataract, conjunctivitis, eye pain, glaucoma.

Other serious adverse reactions which occur rarely (estimated < 0.1%), regardless of causality: Cases reported only in the post-marketing experience are indicated in italics. ***Cardiovascular:*** Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, *vasculitis;* ***GI:*** Intestinal obstruction, intestinal perforation, GI bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus; ***Liver and biliary system:*** Cholelithiasis, *hepatitis, jaundice, liver failure;* ***Hemic and lymphatic:*** Thrombocytopenia, *agranulocytosis, aplastic anemia, pancytopenia, leukopenia;* ***Metabolic:*** *Hypoglycemia;* ***Nervous system:*** Ataxia, suicide; ***Renal:*** Acute renal failure, *interstitial nephritis;* ***Skin:*** *Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis;* ***General:*** Sepsis, sudden death, *anaphylactoid reaction, angioedema.*

Adverse events from analgesia and dysmenorrhea studies: About 1,700 patients were treated with CELEBREX in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies received a single dose of study medication. Doses up to 600 mg/day of CELEBREX were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies. In about 700 patients treated with CELEBREX in the post-general and orthopedic surgery pain studies, the most commonly reported adverse events were nausea, vomiting, headache, dizziness and fever.

OVERDOSAGE
Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. GI bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. Manage patients by symptomatic and supportive care following an overdose. There are no specific antidotes. Dialysis is unlikely to be useful. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful.

DOSAGE AND ADMINISTRATION
Osteoarthritis - 200 mg QD or 100 mg BID.

Rheumatoid arthritis - 100 or 200 mg BID.

Acute Pain and Primary Dysmenorrhea - 400 mg initially followed by an additional 200 mg dose if needed on the first day. On subsequent days, 200 mg BID.

Hepatic Insufficiency: Reduce daily dosage by 50% for patients with moderate hepatic impairment (Child-Pugh Class II).

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References: **1**. Data on file. Searle, a subsidiary of Pharmacia. **2.** Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA*. 1999;282:1921-1928. **3.** Bensen WG, Zhao SZ, Burke TA, et al. Upper gastrointestinal tolerability of celecoxib, a COX-2 specific inhibitor, compared to naproxen and placebo. *J Rheumatol*. 2000;27:1876-1883. **4.** Bensen WG, Agrawal NM, Zhao SZ, et al. Upper gastrointestinal (UGI) tolerability of celecoxib, a COX-2 specific inhibitor, compared to naproxen and placebo [abstract]. Program and abstract of the American College of Rheumatology; November 13-17, 1999; Boston, Mass. Abstract 430.

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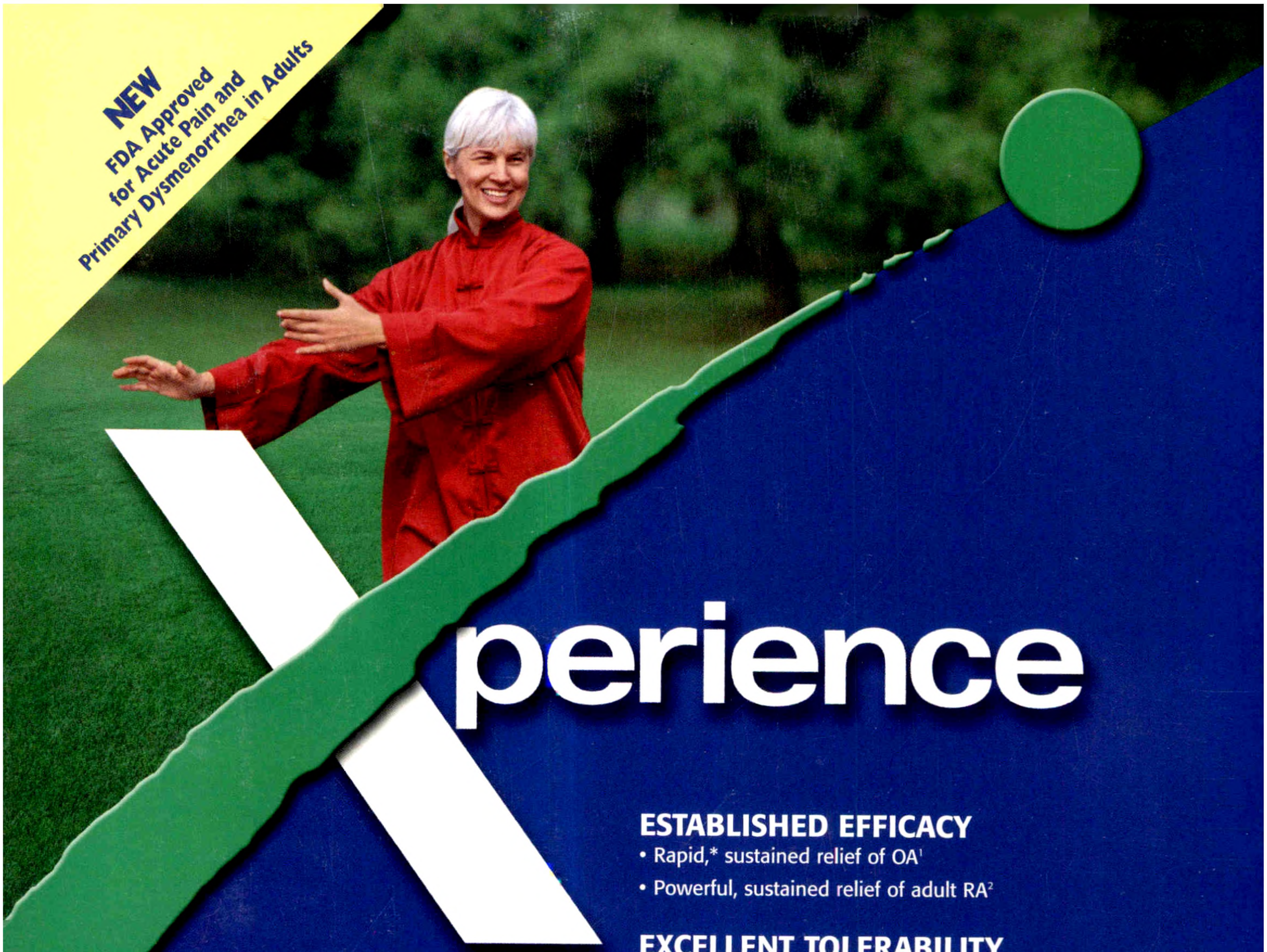

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CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib; in patients who have demonstrated allergic-type reactions to sulfonamides; and in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.

Serious GI toxicity such as bleeding, ulceration, and perforation can occur with or without warning symptoms in patients treated with NSAIDs.

Most common side effects were dyspepsia (8.8% vs 6.2% for placebo), diarrhea (5.6% vs 3.8% for placebo), and abdominal pain (4.1% vs 2.8% for placebo), and were generally mild to moderate.

As with all NSAIDs, CELEBREX should be used with caution in patients with fluid retention, hypertension, or heart failure. NSAIDs may diminish the effects of ACE inhibitors and can reduce the natriuretic effect of furosemide and thiazides.

CELEBREX should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. CELEBREX should be avoided during late pregnancy.

*Significant relief in 24 to 48 hours.

†IMS America. National Prescription Audit. September, 2001.

Please see brief summary of prescribing information and references on next page.

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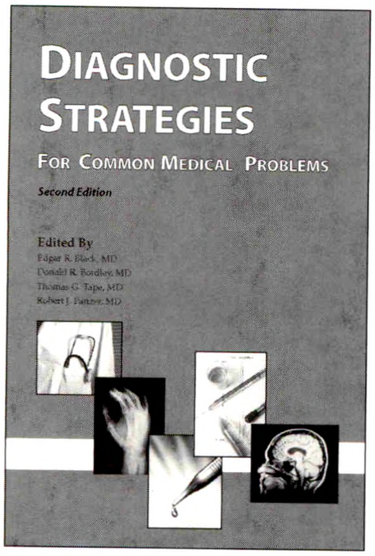

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J.P. Catlett and B.M. Alving

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Dosing Guidelines for Adults

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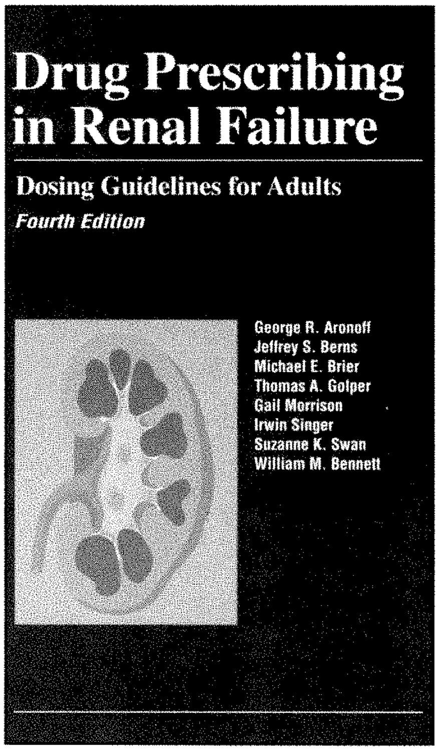

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Annals of Internal Medicine | ARTICLE

Diagnosis of Lower-Limb Deep Venous Thrombosis: A Prospective Blinded Study of Magnetic Resonance Direct Thrombus Imaging

Douglas G.W. Fraser, MRCP; Alan R. Moody, FRCR; Paul S. Morgan, PhD; Anne L. Martel, PhD; and Ian Davidson, FRCR

Background: Current magnetic resonance techniques generate high signal from venous blood and show thrombi as filling defects. Magnetic resonance direct thrombus imaging (MRDTI) directly visualizes acute thrombus.

Objective: To determine the accuracy of MRDTI for diagnosis of acute symptomatic deep venous thrombosis (DVT) below and above the knee.

Design: Prospective, blinded study.

Setting: A 1355-bed university hospital.

Patients: 101 patients with suspected DVT who had had routine venography. Participants were recruited from a cohort of patients with suspected DVT. All patients with a positive venogram and one quarter of patients with a negative venogram were selected by using a random sequence.

Intervention: MRDTI was performed within 48 hours of venography and was interpreted by two reviewers.

Measurements: Diagnosis of DVT overall; isolated calf, femoropopliteal, and ileofemoral DVT; and thrombus in the calf, femoropopliteal, and iliac segments.

Results: The reports from two readers had sensitivities of 96% and 94% and specificities of 90% and 92% for diagnosis of DVT. Sensitivities were 92% and 83% for isolated calf DVT, 97% and 97% for femoropopliteal DVT, and 100% and 100% for ileofemoral DVT. Specificities were 94% and 96% for isolated calf DVT and 100% and 100% for both femoropopliteal and ileofemoral DVT. Similarly, sensitivity and specificity within each of the venous segments ranged from 91% to 100%. Interobserver variability measured by using a weighted κ statistic ranged from 0.89 to 0.98 for these measures.

Conclusion: Magnetic resonance direct thrombus imaging is an accurate noninvasive test for diagnosis of DVT, and its accuracy is maintained below the knee. Comparison of individual venous segments showed that results of MRDTI agreed strongly with findings on venography. Scanning was well tolerated, and interpretation was highly reproducible.

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For author affiliations, current addresses, and contributions, see end of text.

Despite considerable recent advances in diagnostic techniques for lower-limb deep venous thrombosis (DVT), current methods have disadvantages. Ultrasonography, the most accurate noninvasive test, is widely available and cheap. As such, it has largely replaced venography as the test of first choice for symptomatic DVT. In a recent meta-analysis, the sensitivity of ultrasonography was 89% overall for symptomatic DVT and 97% for above-knee thrombosis (1). Large outcome studies have shown that patients may be safely left untreated after a negative result on ultrasonography if they have a low clinical risk score, a low D-dimer level, or a negative result on repeated ultrasonography at 1 week (2–4). However, these strategies may be complex and still require 3% to 34% of outpatients and most inpatients to undergo repeated ultrasonography at 1 week (2–4). In practice, retesting after 1 week is inconvenient, and physicians often rely on a single test or request immediate venography (5). Other problems with ultrasonography include poor sensitivity for asymptomatic disease, difficulties in diagnosing DVT recurrence, and limited visualization in the pelvis (1, 6, 7).

Impedance plethysmography is also commonly used; however, it has a lower diagnostic accuracy than ultrasonography and has similar weaknesses in the setting of recurrent thrombosis, asymptomatic DVT, and DVT below the knee or in the pelvis (1, 4, 6). Computed tomography and magnetic resonance imaging techniques can visualize DVT above the knee and in the pelvis but in general are unsuccessful below the knee (8–10). The ability of these techniques to diagnose DVT recurrence and asymptomatic disease has not been tested.

Venography is the reference standard diagnostic test, but it has in large part been replaced by noninvasive tests. In clinical practice, it is the most reliable test for the diagnosis of asymptomatic thrombosis and thrombosis isolated within the calf or pelvis. However, imaging in the pelvis is inadequate in up to 24% of normal studies, and the proximal extent of thrombosis is fre-

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quently not delineated in patients with above-knee DVT (11). Underfilling of vessels and vessels overlying one another also create problems with venography below the knee. Studies have shown that interobserver variability for venography is high (10% to 16%), especially below the knee ($\kappa = 0.46$ to 0.73 below the knee and 0.46 to 0.84 above the knee) (12, 13). In addition, a high proportion of studies are nondiagnostic for possible DVT recurrence (1, 6).

A noninvasive test is needed that accurately diagnoses above-knee DVT and thrombus below the knee, in the pelvis, and in asymptomatic limbs. Unlike most imaging techniques, which identify thrombus as filling defects, magnetic resonance direct thrombus imaging (MRDTI) visualizes thrombus against a suppressed background (14). In an unblinded comparison with venography, we previously showed that MRDTI precisely visualizes acute deep venous thrombus (14, 15). In the current study, we sought to assess prospectively whether MRDTI is a reliable diagnostic test for suspected acute symptomatic DVT.

METHODS

The ethics committee at our institution granted approval for the study, and all participants gave written informed consent. With the exceptions of pregnant women, patients with known contrast allergy, and those with renal failure, all patients with DVT suspected on the basis of lower limb symptoms are investigated by using venography at our institution. Participants were recruited after routine venography was done between May 1998 and September 1999. During this time, 338 consecutive patients underwent routine contrast venography. Consecutive patients with positive venograms were selected, along with one quarter of those with negative venograms, according to a predetermined random sequence. This protocol was chosen to equalize the numbers of positive and negative cases and was based on a 6-month audit of venograms in our institution that found that 22% of venograms were positive. Clinical diagnostic criteria were not used, and the decision to request investigation for suspected DVT had been made by the attending clinician; however, patients who did not have leg symptoms were not recruited. Other exclusion criteria were failed or inconclusive venography, failed or inconclusive MRDTI, contraindications to MRI, and claustrophobia (**Figure 1**). Individual venous segments that were nondiagnostic at venography were also excluded from analysis.

Magnetic resonance direct thrombus imaging was performed on all patients recruited within 48 hours of venography. The scans were interpreted by an experienced radiologist (reviewer A) and by a nonradiologist (reviewer B) trained to read MRDTI scans. For venograms and MRDTI scans, the reviewers noted the presence or absence of DVT; the diagnostic classification of DVT, divided into isolated calf DVT, femoropopliteal DVT, and ileofemoral DVT; and the presence of thrombus in the calf, femoropopliteal, and iliac venous segments. Venograms were obtained and initially reported by the radiologists on duty. This initial report was used to make recruitment decisions; if the results were discordant with those of MRDTI, ultrasonography was also performed. However, ultrasonography was not used in the calculations of the accuracy of MRDTI. After completion of the study, venograms were interpreted by an independent radiologist, and these results were used as the gold standard against which MRDTI was compared. Results of MRDTI and venography were reported without knowledge of the results of other tests and the other readings. The D-dimer level was measured in all patients at the time of the MRDTI scan by using the Nycocard (Nycomed Pharma AS, Asker, Norway) technique (normal level < 0.3 mg/L).

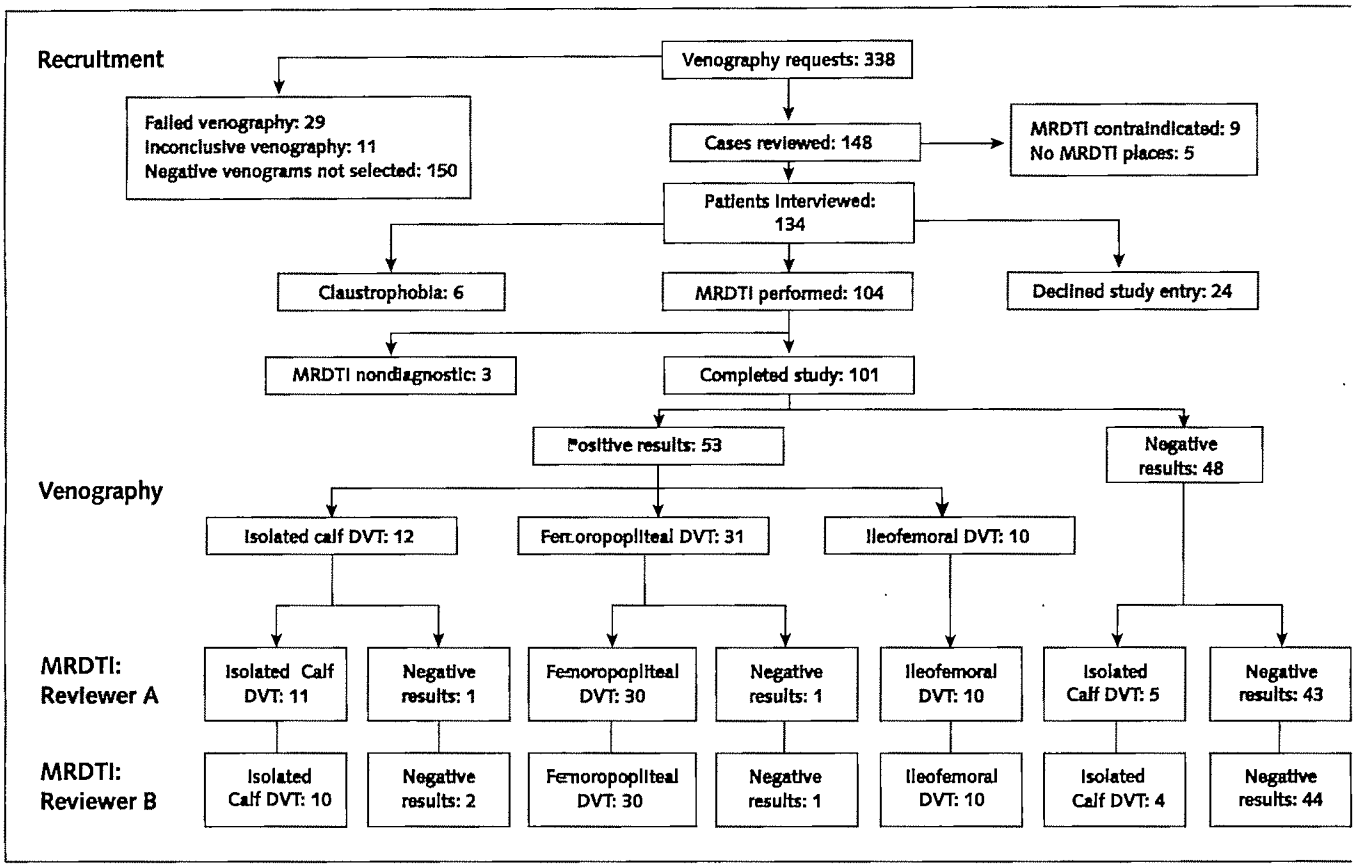
Venography

Venography was performed by cannulating a dorsal pedal vein with a 21-gauge needle and rapidly injecting 50 to 100 mL of iodinated contrast medium (I_2, 300 mg/mL), with the patient supine and tilted 30 degrees with his or her feet downward. A tourniquet was applied above the ankle. Anteroposterior and two oblique views of the deep calf and popliteal veins were obtained. Views of the femoral and iliac veins were then obtained. The study result was considered positive if intraluminal filling defects were seen or persistent nonfilling of veins with a sharp cut-off was detected.

Magnetic Resonance Imaging

Magnetic resonance imaging was performed by using a 1.5-Tesla unit (Siemens Vision, Erlangen, Germany) with a T1-weighted magnetization-prepared

Figure 1. **Outline of the study.**



DVT = deep venous thrombosis; MRDTI = magnetic resonance direct thrombus imaging.

three-dimensional gradient-echo sequence. The sequence included a water-only excitation radiofrequency pulse to abolish the fat signal, and the effective inversion time was chosen to nullify the blood signal. Imaging was performed from the ankle to the inferior vena cava in two imaging blocks with a total acquisition time of 12 minutes by using a 55-cm body coil. Both legs were imaged simultaneously. Scanning was performed by radiographers in all cases. Image assessment involved reading of coronal source data and standard image reconstruction techniques. Acute thrombus was diagnosed on the basis of its high signal against the suppressed background (Figure 2).

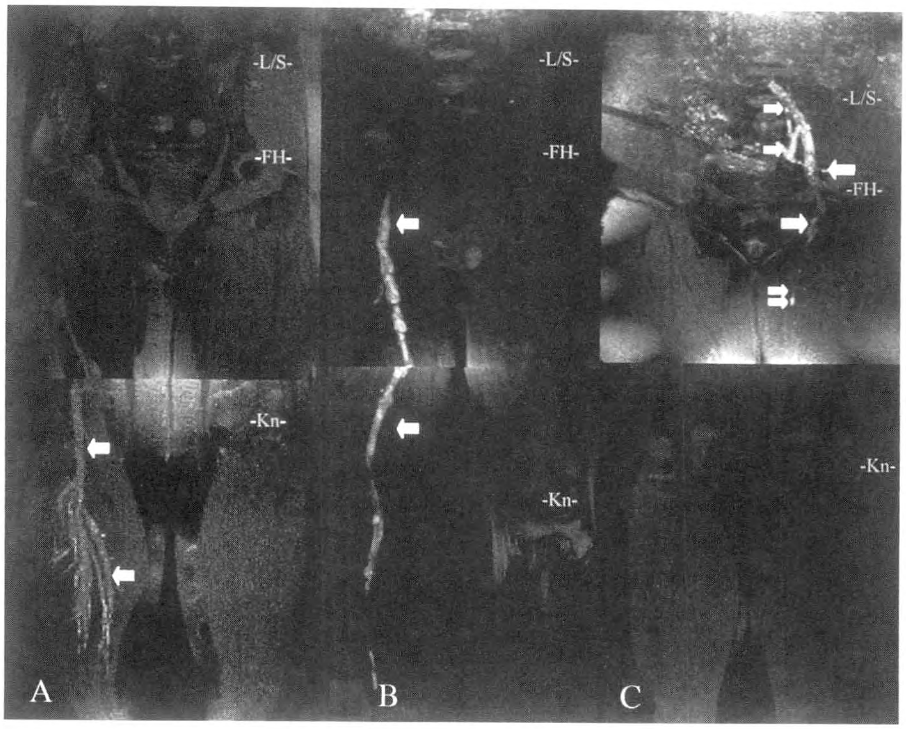
Ultrasonography

Color flow and compression ultrasonographic images of the symptomatic limb from the common femoral vein distally were obtained by using a 5-MHz linear array transducer. As much of the superficial femoral vein as possible was imaged, together with the popliteal vein and the calf veins. Augmentation of flow was used to verify patency. Examinations were performed by senior radiologists, and DVT was confirmed in all cases by noncompressibility on gray-scale images. The sonographer was unaware of the other test results, but in cases of possible isolated calf thrombosis, he or she was told to concentrate the examination below the knee to maximize accuracy in this region.

Statistical Analysis

Sensitivity and specificity were calculated for the overall diagnosis of DVT; diagnosis of isolated calf DVT, femoropopliteal DVT, and ileofemoral DVT; and presence of thrombus in the calf, femoropopliteal vein, and iliac vein. Exact CIs were calculated. Interobserver error was calculated for these observations by us-

Figure 2. **Magnetic resonance direct thrombus imaging in three patients.**



A. Extensive below-knee deep venous thrombosis (DVT) extending into the right popliteal vein (*arrows*). **B.** Large above-knee DVT extending up to the right common femoral vein (*arrows*). Poor fat suppression is seen in the left knee. **C.** Pelvic thrombosis in the left common and internal and external iliac veins, with extension into the common femoral vein (*single arrows*) and long saphenous vein (*double arrow*). FH = femoral head; Kn = knee joint; L/S = lumbosacral joint.

ing the weighted κ statistic with equally spaced weights for positive, nondiagnostic, and negative studies. Confidence intervals for the κ statistic were calculated from asymptotic estimations of the standard error. Calculations were performed by using SPSS software (SPSS, Inc., Chicago, Illinois).

RESULTS

One hundred four patients were recruited according to our protocol (**Figure 1**). The time between venography and MRDTI was less than 8 hours in 28 patients, 8 to 24 hours in 44 patients, and 24 to 48 hours in 32 patients. Age ranged from 20 to 95 years, and symptom onset varied from 1 to 35 days. Ninety-five patients were referred from medical specialties and 9 from surgical specialties; 47 were inpatients and 57 were outpatients. Both reviewers reported that 3 of 5 patients with ipsilateral total hip replacements had nondiagnostic MRDTI scans. Venography diagnosed femoropopliteal DVT in 1 of these patients and was negative in 2 patients. These 3 patients were excluded from further analysis, leaving 101 patients in the study. One patient could tolerate only the first scanning block from ankle to thigh level owing to claustrophobia; however, femoropopliteal DVT could still be diagnosed. All other patients tolerated MRI.

Eighteen of 148 patients (12%) were excluded from the study. Fifteen patients could not undergo MRI because of contraindications (9 patients) or claustrophobia (6 patients), and 3 patients had inconclusive results on MRDTI. Venography failed (29 patients) or was inconclusive (11 patients) in 12% of patients (40 of 338). Venography was inconclusive because of incomplete filling of vessels and difficulties in differentiating acute thrombus from other causes of filling defects. Venography failed owing to unsuccessful venous cannulation, which was related to lower-limb edema or obesity in most cases.

The overall sensitivities of reviewers A and B in diagnosing DVT were 96% (95% CI, 89% to 99%; 51 of 53 tests) and 94% (CI, 86% to 98%; 50 of 53 tests). Corresponding specificities were 90% (CI, 79% to 96%; 43 of 48 tests) and 92% (CI, 82% to 97%; 44 of 48 tests). The overall interobserver error according to the weighted κ statistic was 0.94 (CI, 0.88 to 1.00)

The **Table** shows the sensitivity and specificity of MRDTI for diagnosing isolated calf DVT, femoropopliteal DVT, and ileofemoral DVT. There were two MRDTI tests that both reviewers reported as falsely negative and four MRDTI tests that both reviewers reported as falsely positive compared with venography. On venography, one of the two false-negative MRDTI studies was diagnosed as isolated calf DVT, and one was diagnosed as isolated popliteal vein thrombosis. The patient with isolated calf DVT had a D-dimer level that was not elevated (0.1 mg/L), and ultrasonography found no evidence of thrombosis. Anticoagulation was withheld, and no clinical events were recorded after 9 months. The patient with isolated popliteal vein thrombosis had a D-dimer level that was undetectable on our assay (<0.1 mg/L), but ultrasonographic findings concurred with those on venography. This patient had had a large ipsilateral above-knee DVT 6 months earlier. The false-positive MRDTI studies had all been classified as isolated calf vein thrombosis. Magnetic resonance MRDTI detected a 1-mL thrombus in one of these patients, and ultrasonography was negative. In the remaining three patients, MRDTI diagnosed thrombosis in the gastrocnemius veins (**Figure 3**). Ultrasonography also diagnosed isolated gastrocnemius vein thrombosis in these patients. At 1 week, one of the three patients was breathless; magnetic resonance pulmonary angiography detected multiple pulmonary emboli, and repeated MRDTI diagnosed thrombus progression in the leg. A fifth false-positive result, reported by reviewer A, was a superficial short saphenous vein thrombus misdiagnosed as being within a deep calf vein.

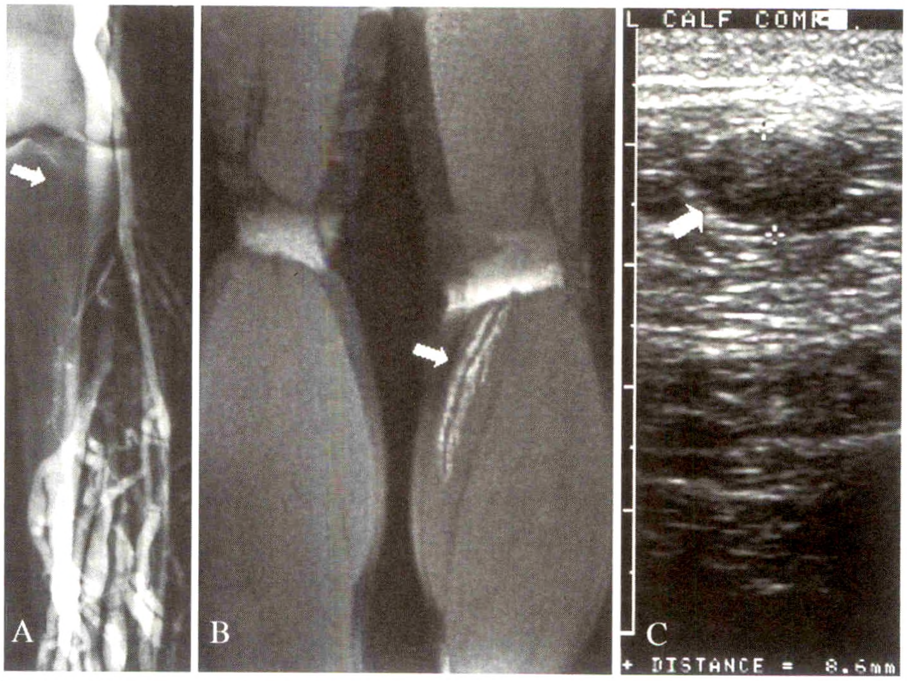
The sensitivity and specificity of MRDTI for the presence of thrombus in the calf and in the femoropopliteal and iliac segments are shown in the **Table**. Venography showed calf thrombosis in 48 patients. Twelve of these patients (described above) had isolated calf DVT. In 36 patients, venography diagnosed calf vein thrombosis associated with above-knee thrombosis. Magnetic resonance direct thrombus imaging diagnosed calf and above-knee thrombosis in 35 of these patients and diagnosed femoropopliteal thrombosis but not calf vein thrombosis in 1 patient. The latter patients had had symptoms for more than 4 weeks before diagnosis. Magnetic resonance direct thrombus imaging correctly iden-

Table. **Sensitivity and Specificity of Magnetic Resonance Direct Thrombus Imaging for Diagnosis of Deep Venous Thrombosis in Different Locations and Segments***

Disease or Segment	Sensitivity [95% CI]†		Specificity [95% CI]†		Interobserver Error [95% CI]‡
	Reviewer A	Reviewer B	Reviewer A	Reviewer B	
	← % (n/n) →				
Diagnosis					
Isolated calf DVT	92 [66–100] (11/12)	83 [56–97] (10/12)	94 [88–98] (84/89)	96 [90–98] (85/89)	0.89 [0.78–1.0]
Femoropopliteal DVT	97 [85–100] (30/31)	97 [85–100] (30/31)	100 [95–100] (70/70)	100 [95–100] (70/70)	0.98 [0.94–1.0]
Ileofemoral DVT	100 [74–100] (10/10)	100 [74–100] (10/10)	100 [97–100] (91/91)	100 [97–100] (91/91)	0.94 [0.82–1.0]
Segment					
Calf veins	96 [87–99] (46/48)	94 [84–98] (45/48)	91 [81–96] (48/53)	93 [84–97] (49/53)	0.94 [0.91–1.0]
Femoropopliteal	98 [89–100] (40/41)	98 [89–100] (40/41)	100 [95–100] (60/60)	100 [95–100] (60/60)	0.98 [0.94–1.0]
Iliac veins	100 [74–100] (10/10)	100 [74–100] (10/10)	100 [96–100] (77/77)	100 [96–100] (77/77)	0.94 [0.82–1.0]

* Venography was used as the gold standard. DVT = deep venous thrombosis.
† The number of patients used to calculate the percentage is shown in parentheses.
‡ Weighted κ statistic.

Figure 3. **Venography, magnetic resonance direct thrombus imaging, and ultrasonography in a patient with gastrocnemius thrombus.**



A. Venogram. The gastrocnemius veins have not been visualized (*arrow*). **B.** Magnetic resonance direct thrombus imaging. The technique demonstrates high-signal filling paired gastrocnemius veins (*arrow*). **C.** Ultrasonographic image. This image under compression shows a gastrocnemius vein filled with thrombus (*arrow*).

tified femoropopliteal thrombosis in 30 of 31 cases of femoropopliteal DVT. In 14 of these patients, venography failed to visualize the iliac veins. These cases were categorized as femoropopliteal DVT, and the iliac segments were excluded from the segmental comparison with MRDTI. Both iliac and femoropopliteal thrombosis were correctly identified in 10 patients with ileofemoral DVT.

The four false-positive cases of isolated calf vein thrombosis were the only false-positive venous segments. However, the iliac veins were not visualized on venography in several cases diagnosed as femoropopliteal thrombosis (see below).

The iliac veins were not visualized on venography in 14 patients with femoral thrombosis. Magnetic resonance direct thrombus imaging demonstrated extension into the iliac veins in 3 of these patients and extension into the inferior vena cava as far as the renal veins in 1 patient. In addition, venography did not define the upper extent of thrombosis in 9 of 10 patients with ileofemoral DVT. Magnetic resonance direct thrombus imaging showed extension into the inferior vena cava in 3 of these patients. Greater proximal extension into the iliac vein or inferior vena cava was therefore demonstrated by MRDTI in 7 of 41 (17%) patients with above-knee DVT. These findings are observational only and were not validated by using any other technique.

Magnetic resonance direct thrombus imaging also diagnosed asymptomatic contralateral thrombosis in 9 of 53 (17%) patients with DVT and 1 postoperative patient with no thrombus in the symptomatic leg. In the latter patient, venography of the asymptomatic leg was performed and below-knee DVT was confirmed.

DISCUSSION

In unselected patients presenting with suspected acute symptomatic DVT, MRDTI was highly sensitive and specific for diagnosis of DVT overall and for the

]

individual diagnoses of isolated calf DVT, femoropopliteal DVT, and ileofemoral DVT. Similarly, a separate comparison of the venous segments showed that MRDTI reliably diagnosed thrombosis in the calf, femoropopliteal, and iliac vessels. Interpretation of MRDTI was highly reproducible between observers, and κ values were significantly higher than those reported for venography (12, 13).

Patients were drawn from consecutive venogram requests made by clinicians who suspected DVT on the basis of leg symptoms. Exclusion criteria were designed only to exclude patients who could not undergo MRI and those who had nondiagnostic test results. Symptom duration and age range varied widely, and the case-mix included representative proportions of inpatients and surgical patients. Magnetic resonance direct thrombus imaging was compared with the accepted reference standard of venography, and venograms were read by an independent radiologist. Magnetic resonance direct thrombus imaging scans were reported by both a radiologist and a nonradiologist, without knowledge of other test results. Exact CIs were calculated in all instances.

Selection of one quarter of patients with negative venograms allowed us to include more patients with positive results and to separately assess isolated below-knee DVT, femoropopliteal DVT, and ileofemoral DVT. The overall specificity for the diagnosis of DVT is valid. However, the higher proportion of positive cases than in the recruitment population affected the assessment of specificity for the diagnoses of isolated calf, femoropopliteal, and ileofemoral DVT and for the individual venous segments.

The small numbers of patients with isolated calf thrombosis and ileofemoral thrombosis produced wide CIs for these diagnoses. However, calf thrombosis associated with above-knee thrombosis was accurately diagnosed. In addition, further analysis suggests that the venographic diagnosis was erroneous in three patients in whom MRDTI diagnosed thrombosis in the gastrocnemius veins and venography was negative. Noncompressibility was clearly demonstrated by ultrasonography in the gastrocnemius veins in these patients, whereas venographic contrast had failed to fill these vessels. Although ultrasonography has poor sensitivity below the knee, its specificity remains high (90% to 100%), and the gastrocnemius veins, which are near the skin surface, are not difficult to image (6). Poor filling of the gastrocnemius veins is common in venography, especially if ankle tourniquets are used, and may occur in up to 75% of studies (11, 16). Moreover, thrombus progression and pulmonary embolism occurred at 1 week in one of these patients. Although venography is considered the most reliable test below the knee, its inaccuracies are well known, and error rates are most pronounced below the knee because of inadequate filling and overlying vessels (12, 13, 17).

Above-knee MRDTI was falsely negative compared to venography in one patient. Ultrasonography confirmed the venographic diagnosis of isolated popliteal vein thrombosis. However, the patient had had ipsilateral femoropopliteal thrombosis 6 months earlier, and both ultrasonography and venography discriminate poorly between acute and chronic thrombus. The low D-dimer level may suggest that ultrasonography and venography demonstrated persistent filling defects from the previous DVT that would not have been visualized on MRDTI.

Assessment of the accuracy of a new diagnostic test against an imperfect gold standard is problematic. The accuracy of the new test will be underestimated if its errors are independent of those of the reference test and will be overestimated if the errors are not independent (18). Thrombus is visualized by venography as filling defects in veins that are opacified by using contrast; inaccuracies are caused by incomplete filling of vessels with contrast, overlying vessels, and difficulties in differentiating acute thrombus from other causes of filling defects (principally chronic thrombus). Magnetic resonance direct thrombus imaging visualizes thrombus directly; venous blood is not imaged, and thrombus more than 6 months old is not visualized. Therefore, the errors of MRDTI and venography are likely to be independent, and our study probably underestimated the accuracy of MRDTI.

Consideration of the results of ultrasonography and D-dimer measurement is therefore relevant when results of MRDTI and venography are discordant. Revision of the reference diagnosis according to results of ultrasonography in the discordant cases would increase the overall sensitivity to 98% (54 of 55 tests interpreted by reviewer A) and 96% (53 of 55 tests interpreted by reviewer B), with an overall specificity of 96% (44 of 46 tests interpreted by reviewer A) and 98% (45 of 46 tests interpreted by reviewer B). The reported sensitivity of MRDTI for isolated calf thrombosis increases to 100% (14 of 14 tests interpreted by reviewer A) and 93% (13 of 14 tests interpreted by reviewer B), and the reported specificity increases to 98% (85 of 87 tests by reviewer A) and 99% (86 of 87 tests by reviewer B) The estimated accuracy for femoropopliteal and ileofemoral thrombosis would remain unchanged. However, the use of a second reference test only in the discordant cases and the poor sensitivity of ultrasound in the calf veins would tend to overestimate the sensitivity of MRDTI for isolated calf vein thrombosis in this analysis. We therefore used venography as the reference standard and discussed the discordant cases in full. A limitation of our study is the lack of D-dimer and ultrasonography results in the cases in which results of MRDTI and venography were concordant.

Venography was inconclusive in 11 patients, again principally owing to inadequate filling of vessels and problems in differentiating acute from chronic thrombus. Venography failed in 29 patients in whom unsuccessful venous cannulation was related to tissue oedema and obesity. Because MRDTI would not be expected to be less reliable in these cases, their exclusion probably did not affect the estimated accuracy of MRDTI.

The sensitivity and specificity of MRDTI, a noninvasive test, were high below the knee and in the pelvis. Current MRI techniques have high accuracy in the ileofemoral veins but cannot image vessels with slow flow below the knee. They are also susceptible to flow artifacts, and imaging times may be long (19, 20). More invasive computed tomography and MRI techniques that use injection into the symptomatic foot visualize the deep veins below and above the knee but share many of the problems of conventional venography (21, 22).

Most current imaging techniques require all of the deep veins to be visualized so that thrombus in them can be excluded. This is most straightforward for the superficial and common femoral veins and the popliteal vein, which are usually single vessels; accuracy is high in these veins. However, sensitivity is much lower for the multiple small veins below the knee and for the more inaccessible pelvic and deep femoral veins (7, 11). Impedance plethysmography has similar problems, but for different reasons. Magnetic resonance direct thrombus imaging differs fundamentally from these techniques because acute thrombus is directly visualized. Interpretation of studies involves a search for regions of high signal and does not require visualization of unaffected veins. Thus, a nonradiologist can interpret MRDTI scans accurately and rapidly. Signal generation does not depend on blood flow or filling of vessels with contrast. Flow artifacts, low flow rates in small veins, and venous occlusion due to extrinsic compression or chronic thrombus thus do not affect the technique. However, other causes of high signal must be distinguished from DVT; these include thrombus in other structures (hematomas or arterial thrombus); failure of the water excitation pulse to remove fat signal; and fast inflow of blood at the edge of the imaging block, which can also generate high signal for several centimeters within arteries. The use of standard multiplanar reconstruction techniques allows differentiation of these other causes of high signal from venous thrombosis.

Visualization of thrombus depends on the T1 shortening that occurs after blood clots. This T1 shortening is caused by methemoglobin production (23). The onset of the T1 reduction in intracranial hematomas is delayed by up to 7 days, and we were concerned that very fresh thrombosis may have been missed in the acute phase. However, we did not observe this in the current study, and it has been shown that high signal is visible within 8 hours of the onset of symptoms (14). Intravascular methemoglobin production is probably much more rapid than in hematomas. Similarly, high signal in DVT lasts from several weeks to several months, whereas high signal in intracranial hematomas may last more than 1 year (23). In the current study, above-knee DVT only was diagnosed by using MRI in one patient who presented at 33 days, but venography also demonstrated filling defects below the knee. This below-knee thrombus may have lost its high signal by the time of scanning. However, the duration of symptoms in the two false-negative cases was not notably long or short, and MRDTI diagnosed DVT despite wide variation in the duration of symptoms.

Access and cost of MRI may limit widespread use of MRDTI at present. Typical commercial charges for ultrasonography and unilateral venography are $300 (range, $200 to $500) and $450 (range, $250 to $800), respectively (24). The cost of MRI depends on the duration of the scan and the use of contrast. A typical commercial charge for an MRI scan without contrast that requires a scanning time of 40 to 60 minutes would be $1000, whereas more rapid sequences may cost considerably less (25–27). Magnetic resonance direct thrombus imaging is performed on a standard clinical scanner, requires no special patient preparation, does not require contrast, and had a scanning time of 12 minutes in our study. Scanning time may be reduced to 7 minutes without degradation of image quality. Therefore, the cost of MRDTI should be similar to that of venography. Magnetic resonance direct thrombus imaging cannot be done in patients with contraindications to MRI, those with claustrophobia, and those who cannot lie flat.

Magnetic resonance direct thrombus imaging may have a specific role in several scenarios. Deep venous thrombosis in pregnancy is frequently pelvic in origin, and in our experience, MRDTI is both successful and well tolerated in pregnancy (28). The full extent of thrombosis can be assessed noninvasively in patients with ileofemoral DVT who may be candidates for thrombolysis (**Figure 2**). Magnetic resonance imaging can be done without difficulty in patients with full-length leg plaster casts. In addition, because it is noninvasive, carries no exposure to ionizing radiation or contrast agents, and provides comprehensive imaging of the full extent of thrombosis, MRDTI is well suited for repeated testing to monitor thrombus progression or for use in natural history or therapeutic trials.

The time course of the high signal in MRDTI allows confident diagnosis of acute thrombus and may also allow exclusion of fresh thrombosis in cases of DVT recurrence. Conventional tests are often inconclusive in this setting because the age of filling defects cannot be determined. At 6 months, 43 of the patients in this study with initially positive MRDTI scans were rescanned; no patient had remaining regions of high signal, despite persistent deep venous occlusion on ultrasonography in some of these patients (data not shown). Therefore, the presence of high signal from thrombus indicates that the thrombus is less than 6 months old. In addition, we have shown that changes in the pattern of high signal during the first few weeks after formation allows accurate determination of thrombus age (29).

Asymptomatic DVT was detected in the contralateral leg in 10 patients. Conventional noninvasive tests have poor sensitivity for asymptomatic thrombosis, which is frequently small and localized and does not obstruct the lumen (1, 6). Magnetic resonance direct thrombus imaging can image small-volume thrombi and does not depend on filling of the lumen or obstruction to blood flow. Therefore, MRDTI would probably be a reliable test for asymptomatic thrombosis. Combined with magnetic resonance pulmonary embolus imaging, MRDTI could therefore be an important research tool (30). Because imaging times are becoming shorter, the cost of MRDTI could soon be similar to that of other noninvasive tests (31, 32). Current protocols allow at least four patients to be scanned per hour.

In summary, current imaging methods for the diagnosis of DVT have disadvantages. Magnetic resonance direct thrombus imaging is noninvasive, does not require contrast agent, and is highly accurate and reproducible. Its accuracy is maintained both in the calf and pelvis, and sensitivity and specificity below the knee are high. Magnetic resonance direct thrombus imaging has promising roles in the diagnosis of DVT in pregnancy and demonstration of the full extent of thrombosis in high-risk patients. It is also well suited for diagnosis of recurrent thrombosis and asymptomatic disease and as a powerful research tool. Lack of widespread availability of MRI and cost limit use of MRDTI at present. However, as scanners become more plentiful and scanning speed increases, costs will decrease and may become similar to those of other noninvasive tests.

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ARTICLE

Initial Evaluation of Rectal Bleeding in Young Persons: A Cost-Effectiveness Analysis

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Background: Evaluation of rectal bleeding in young patients is a frequent diagnostic challenge.

Objective: To determine the relative cost-effectiveness of alternative diagnostic strategies for young patients with rectal bleeding.

Design: Cost-effectiveness analysis using a Markov model.

Data Sources: Probability estimates were based on published medical literature. Cost estimates were based on Medicare reimbursement rates and published medical literature.

Target Population: Persons 25 to 45 years of age with otherwise asymptomatic rectal bleeding.

Time Horizon: The patient's lifetime.

Perspective: Modified societal perspective.

Interventions: Diagnostic strategies included no evaluation, colonoscopy, flexible sigmoidoscopy, barium enema, anoscopy, or any feasible combination of these procedures.

Outcome Measures: Life expectancy and costs.

Results of Base-Case Analysis: For 35-year-old patients, the no-evaluation strategy yielded the least life expectancy. The incremental cost-effectiveness of flexible sigmoidoscopy compared with no evaluation or with any strategy incorporating anoscopy (followed by further evaluation if no anal disease was found on anoscopy) was less than $5300 per year of life gained. A strategy of flexible sigmoidoscopy plus barium enema yielded the greatest life expectancy, with an incremental cost of $23 918 per additional life-year gained compared with flexible sigmoidoscopy alone.

Results of Sensitivity Analysis: As patient age at presentation of rectal bleeding increased, evaluation of the entire colon became more cost-effective. The incremental cost-effectiveness of flexible sigmoidoscopy plus barium enema compared with colonoscopy was sensitive to estimates of the sensitivity of the tests. In a probabilistic sensitivity analysis comparing flexible sigmoidoscopy with anoscopy followed by flexible sigmoidoscopy if needed, the middle 95th percentile of the distribution of the incremental cost-effectiveness ratios ranged from flexible sigmoidoscopy yielding an increased life expectancy at reduced cost to $52 158 per year of life gained (mean, $11 461 per year of life saved).

Conclusions: Evaluation of the colon of persons 25 to 45 years of age with otherwise asymptomatic rectal bleeding increases the life expectancy at a cost comparable to that of colon cancer screening.

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Colorectal cancer is the third most common cause of cancer-related death in men and women (1). The incidence increases with increasing age, and before 40 years of age, the risk for colorectal cancer is low (2). The disease can be effectively prevented by endoscopic removal of precancerous adenomatous polyps (3). After invasive cancer develops, mortality from colorectal cancer increases with advancing cancer stage at diagnosis (1). Most medical professional societies recommend routine screening with fecal occult blood testing, flexible sigmoidoscopy, colonoscopy, or barium enema beginning at 50 years of age for average-risk patients and 40 years of age for persons at increased risk (1).

Rectal bleeding occurs in approximately 20% of the population annually (4–9) and most commonly results from benign anal disorders (10–14). However, when rectal bleeding is caused by a colorectal neoplasm, expedient evaluation may result in earlier detection of the neoplasm and reduced cancer-related mortality. Most studies examining the risk for colonic neoplasm in patients with rectal bleeding have been conducted predominantly in patients older than 40 years of age (10, 11, 15, 16). The probability that rectal bleeding results from a colorectal neoplasm is much lower in younger patients than in older patients. Many investigators recommend evaluation of the entire colon of older adults with rectal bleeding (10, 11, 15, 16). Rigorous evaluation of the potential risks, benefits, and costs of such a strategy in younger patients has not been reported. Thus, when faced with a young patient with rectal bleeding, clinicians must weigh the potential benefits of identifying and removing relatively rare but potentially fatal colonic neoplasms versus the potential complications and costs associated with diagnostic and therapeu-

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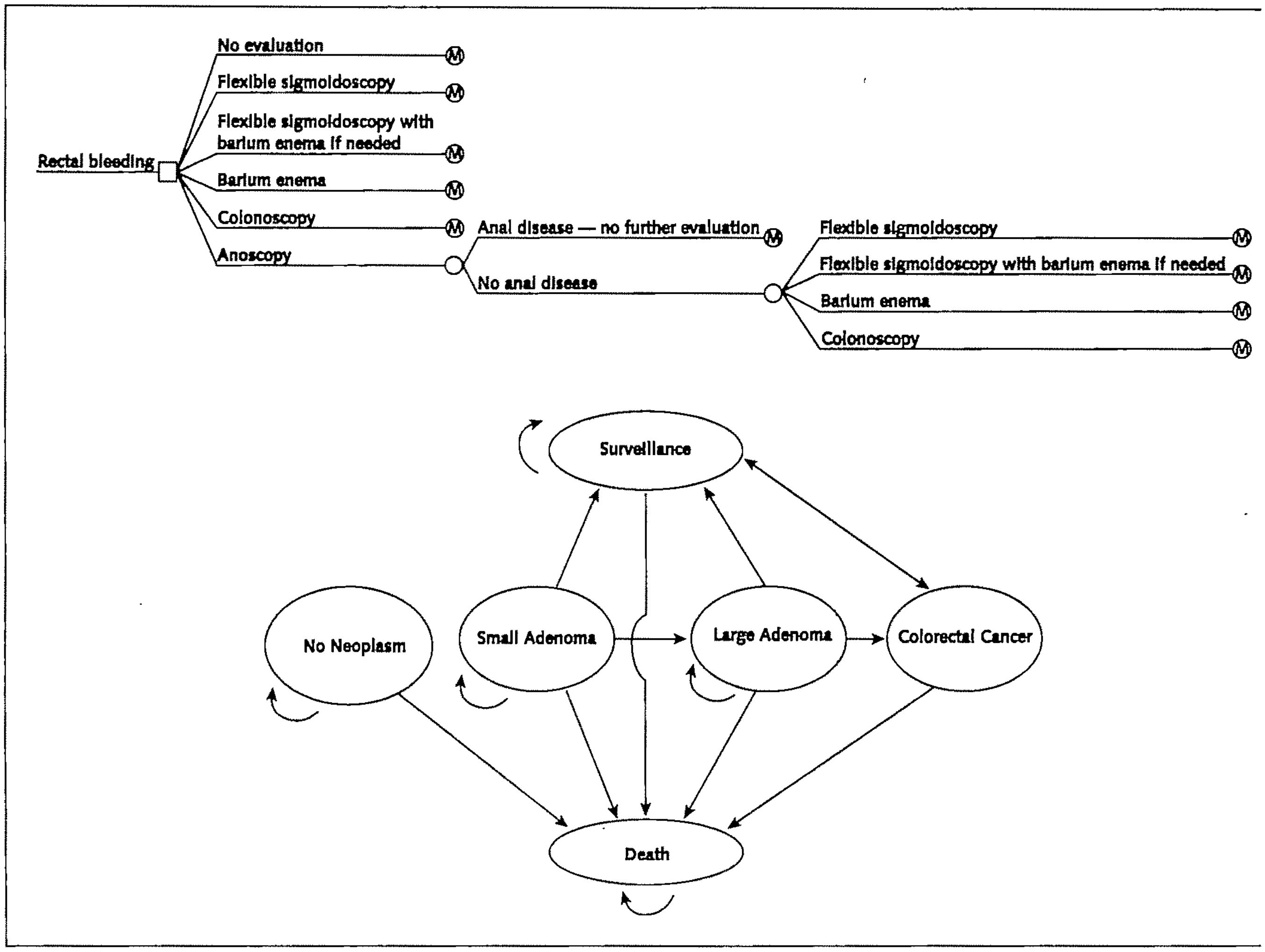
Figure 1. **Overview of the Markov model.**



Top. The alternative diagnostic strategies. Patients with rectal bleeding undergo no evaluation, undergo anoscopy, or undergo a diagnostic test. Patients undergoing anoscopy are referred for further diagnostic testing only if no lesions are identified on anoscopy. All patients with colitis eventually undergo colonoscopy. The circled "M" notations represent Markov nodes in the computer program. Bottom. The potential consequences of colonoscopy. Patients with detected adenomas or who survive cancer therapy enter surveillance programs. Undetected adenomas may remain as adenomas or may advance to cancer. Adenomas and cancers may also be detected at the time of colorectal cancer screening.

tic tests. We assessed the relative survival and cost-effectiveness of using alternative diagnostic strategies for young persons with otherwise asymptomatic rectal bleeding.

METHODS

We developed a Markov analytic decision model (**Figure 1**) to represent the natural history of patients with rectal bleeding. The base model consisted of a 35-year-old patient presenting with otherwise asymptomatic rectal bleeding, which we defined as blood in the toilet bowl, on the tissue paper, or mixed with stool. A patient could follow one of nine strategies: no evaluation, flexible sigmoidoscopy, air-contrast barium enema, flexible sigmoidoscopy and air-contrast barium enema, colonoscopy, anoscopy followed by flexible sigmoidoscopy, anoscopy followed by air-contrast barium enema, anoscopy followed by flexible sigmoidoscopy and air-contrast barium enema, or anoscopy followed by colonoscopy. The model assumed that patients who underwent anoscopy were further evaluated by using an-

Table 1. **Probability Estimates Included in the Model**

Variable	Base Estimate (Range)	Reference
5-year relative survival rate		
With local-stage colorectal cancer	0.914*	17
With regional-stage colorectal cancer	0.661*	17
With advanced-stage colorectal cancer	0.085*	17
Annual mortality from other causes	Age-specific	18
Perforation from barium enema	0.00005 (0.00001–0.0001)	1
Perforation from colonoscopy	0.001 (0.0001–0.002)	1
Perforation from flexible sigmoidoscopy	0.00015 (0.0001–0.0002)	1
Hemorrhage after polypectomy	0.006 (0.00001–0.012)	19, 20
Perforation from polypectomy	0.003 (0.001–0.005)	19, 21–25
Die as a result of a perforation	0.015 (0.001–0.03)	1
Prevalence of neoplasm†		
At age 25 y	0.005 (0.001–0.01)	26–29
At age 35 y	0.03 (0.01–0.05)	26–29
At age 45 y	0.15 (0.1–0.2)	26–29
Colonic neoplasm within the reach of flexible sigmoidoscopy	0.80 (0.65–0.90)	1, 30–33
Relative prevalence of isolated nonadenomatous polyps‡	0.73 (0.0001–2.0)	32–34
Proportion of nonadenomatous polyps within reach of flexible sigmoidoscopy	0.70 (0.5–1.0)	35, 36
Increased risk for neoplasms in persons with rectal bleeding	2.0 (1.0–3.0)	30, 31, 37, 38
Proportion of polyps > 9 mm at time of bleeding	0.16 (0.10–0.22)	10, 11, 39–41
Colonic neoplasm contains invasive cancer	0.002 (0.001–0.004)	17
Cancer is local stage at time of bleeding	0.50 (0.3–0.7)	17
Cancer is regional stage at time of bleeding	0.25 (0.15–0.35)	17
Symptoms from undiagnosed local-stage cancer	0.18 (0.10–0.26)	17, 30, 31
Symptoms from undiagnosed regional-stage cancer	0.63 (0.46–0.80)	17, 30, 31
Symptoms from undiagnosed distant-stage cancer	1.00 (1.0–1.0)	17, 30, 31
Small polyp advances to large polyp	0.05 (0.01–0.09)	1, 26, 42
Large polyp advances to local-stage cancer	0.03 (0.01–0.05)	1, 26, 42
Prevalence of anal disease§	0.70 (0.5–0.9)	9, 10, 12, 13, 43–46
Prevalence of colitis	0.05 (0.01–0.09)	10, 11, 13, 43–45
Relative risk for colonic neoplasm in patients with anal disease	0.60 (0.3–0.9)	11, 12, 47
Sensitivity of barium enema for small neoplasms	0.65 (0.50–0.80)	1
Sensitivity of barium enema for large neoplasms	0.80 (0.70–0.90)	1
Specificity of barium enema for neoplasms	0.83 (0.66–1.0)	1
Sensitivity of colonoscopy for small neoplasms	0.78 (0.70–0.85)	1
Sensitivity of colonoscopy for large neoplasms	0.95 (0.90–0.99)	1
Sensitivity of colonoscopy for symptomatic cancer	1.00 (1.0–1.0)	1
Sensitivity of flexible sigmoidoscopy for small neoplasms	0.78 (0.70–0.85)	1
Sensitivity of flexible sigmoidoscopy for large neoplasms	0.95 (0.90–0.99)	1
Sensitivity of colorectal cancer screening for polyps or cancer	0.75 (0.6–0.9)	1, 32, 33
Proportion of patients screened with flexible sigmoidoscopy	0.30 (0.1–0.5)	48
Proportion of screened patients entering colonoscopic surveillance	0.20 (0.1–0.3)	32, 33
Efficacy of cancer surveillance‖	0.995 (0.99–1.0)	1, 3
Proportion of patients with recurrent polyps identified during surveillance	0.45 (0.3–0.5)	49
New distal adenomas at time of screening in patients with previously isolated proximal neoplasm	0.50 (0.0–0.5)	32, 33

* Because of the large sample sizes used in the Surveillance, Epidemiology, and End Results (SEER) program calculations, no variability was assumed for relative survival rates.
† Neoplasm includes adenomatous polyps and colorectal cancer.
‡ Prevalence of isolated nonneoplastic polyps such as hyperplastic polyps relative to neoplastic adenomatous polyps.
§ Anal disease includes hemorrhoids and fissures.
‖ Assumes that 95% of cancers diagnosed during surveillance are local stage, 4.5% are regional stage, and 0.5% are distant stage.

other test only if anoscopy revealed no apparent source of bleeding (such as hemorrhoids) in the anorectal region. The model similarly assumed that patients underwent barium enema after flexible sigmoidoscopy only if sigmoidoscopy had identified no source of bleeding other than anal disease. All patients with a colonic neoplasm identified by using flexible sigmoidoscopy or barium enema were assumed to have subsequently undergone colonoscopy.

Probability Estimates

Table 1 summarizes the source, base-case estimates, and ranges for the probability estimates included in the

Table 2. **Cost Estimates Incorporated in the Model**

Variable	Base Estimate (Range), $
Flexible sigmoidoscopy without biopsy	174.24 (139.11–223.31)
Flexible sigmoidoscopy with biopsy	205.08 (163.47–263.28)
Colonoscopy	606.55 (484.13–777.58)
Polypectomy	254.04 (203.89–323.66)
Pathology review of biopsy specimens	180.78 (68.74–180.78)
Barium enema	186.92 (145.70–245.69)
Care for early-stage cancer	35 000 (25 000–45 000)
Care for advanced-stage cancer	45 000 (35 000–55 000)
Care for perforation during diagnostic procedure	13 032 (13 032–35 000)
Care for postpolypectomy bleeding	4360 (3000–5000)

model. After reviewing previous autopsy studies, Koretz (26) estimated that the prevalence of colonic neoplasms in persons 30 to 39 years of age was 0.04 for men and 0.02 for women (26). On the basis of studies of rectal bleeding in patients of all ages with colorectal cancer and polyps (30, 31, 37, 38), we estimated for our analyses that patients with rectal bleeding had a twofold increased prevalence of neoplasms. In addition, on the basis of studies of patients of all ages (9, 12, 14, 29), we assumed that patients with rectal bleeding patients and anal disease (hemorrhoids or anal fissures) identified at anoscopy were less likely than patients with rectal bleeding but without anal disease to have neoplastic lesions. In the base-case analysis, we assumed that the prevalence of neoplasms in patients with rectal bleeding and anal disease was 40% lower than that in patients with bleeding and no anal disease. Thus, in our base-case analysis, 70% of the rectal bleeding population was considered to have anal disease, and in this group, the prevalence of colonic neoplasms was estimated to be 0.036 (1.2 times that of the general population); in the 30% of the rectal bleeding population with no anal disease, the prevalence of colonic neoplasms was considered 0.06 (2.0 times that of the general population). The overall prevalence of neoplasms in persons with rectal bleeding was estimated to be 0.0432 (1.44 times that of the general population). This estimate is close to the prevalence of colonic neoplasms (0.043) reported in an endoscopic study of young persons with rectal bleeding (27). The Appendix shows the formula that we used to calculate the prevalence of neoplasms.

Several investigators have previously estimated the time required for benign adenomas to become invasive cancer (1, 26, 42). In our model, we divided neoplasms into small adenomas (diameter < 10 mm), large adenomas, and invasive cancer. We assumed a constant annual probability that small adenomas would advance to large adenomas and that large adenomas would advance to cancer. By using the base-case estimates, we determined that approximately 9% of polyps present at the time of bleeding would progress to cancer in 10 years and that approximately 22% would progress in 20 years. Similarly, in the base case, the incidence of cancer diagnosed in the no-evaluation group was 2.1 times the expected rate for the U.S. population at 5 years and subsequently decreased toward normal (17).

Cost Estimates

The model used a modified societal perspective by including all direct medical costs (**Table 2**) regardless of who incurred the cost. Indirect costs, such as time lost from work, were not included. For the direct costs of diagnostic procedures, including physician and facility fees, we assumed that procedures were performed in an outpatient setting. We estimated the physician fees on the basis of the median fees for U.S. physicians for 2000. We based the ranges for sensitivity analyses on the maximum and minimum physician fees and based facility fees on the national average allowable charge by Medicare for 1998 (Gant G. Personal communication). In determining the cost of a surveillance colonoscopy, we assumed that 45% of patients would require polypectomy (49). We estimated the cost of caring for patients with colorectal cancer on the basis of a recent National Cancer Institute–sponsored study (50) of the costs of treating patients in the Kaiser Foundation Health Plan. All costs for treating colorectal cancer were assumed to be incurred during the first year after diagnosis. The cost for pathology review of biopsy specimens and the costs for the management of perforations and bleeding after polypectomy were based on a recent cost-effectiveness model that used Medicare reimbursement rates (51). We did not include the cost of office visits for rectal bleeding or for anoscopy because we assumed that these costs would be incurred regardless of treatment strategy (the model begins after the initial office visit). We applied a 3% discount rate to costs and benefits (52).

Additional Assumptions Included in the Model

In the model, we did not account for the progression of new polyps over time, although we did account for the occurrence of new polyps identified in patients undergoing cancer screening. On the basis of current understanding of the adenoma–carcinoma sequence, a new polyp probably would not advance to invasive cancer more rapidly than a polyp present at the time of bleeding. Thus, the model depicted the effect of the diagnostic strategies on the natural history of the polyps and cancers present at the time of first bleeding.

The model assumed that all patients with bleeding secondary to colitis would undergo colonoscopy in the first 2 years of symptoms as a result of persistent or worsening symptoms or as follow-up to flexible sigmoidoscopy or barium enema.

The model assumed that without therapy, local-stage cancer would advance to regional-stage cancer within 2 years and that regional-stage cancer would advance to distant-stage cancer within 1 year. The model also assumed that all cases of advanced-stage cancer were diagnosed during the first year as a result of screening or symptoms.

The model assumed that screening with flexible sigmoidoscopy would be offered every 5 years, beginning at age 50 years, but assumed that only some patients would agree to undergo screening. We assumed that surveillance colonoscopy was performed every 5 years after the diagnosis of adenomatous polyps or cancer.

Quality of Life

We did not assign quality-of-life estimates to the different health states in the primary model because limited data were available. However, in sensitivity analyses, we assumed that during the first 5 years after diagnosis, quality of life would decrease by 5% for patients with local or regional cancer and would decrease by 20% for patients with distant cancer.

Analysis

We report the results of the cost-effectiveness analyses as incremental cost-effectiveness, which we defined as the increase in cost necessary to yield a 1-year increase in survival compared with the alternative strategy. We performed one-way sensitivity analyses across the range of variables in the model and performed two-way analyses to examine the relationship of test sensitivity on the incremental cost-effectiveness ratio.

We used a Monte Carlo simulation to examine the variability in the incremental cost-effectiveness ratios while allowing all probability estimates to vary simultaneously. In this analysis, we performed 1000 trials. In each trial, the values for each probability variable were sampled once from across the full range of potential values. The logit normal distribution was assumed for probabilities. An infinite number of persons were then simulated for each trial to obtain the mean cost and effectiveness values for the trial. We then calculated the mean, standard deviation, and range of the middle 95th percentile (from the 2.5th to the 97.5th percentiles) for the distribution of incremental cost-effectiveness ratios. Because costs of procedures tend not to vary within a single location, we used fixed cost estimates in these analyses.

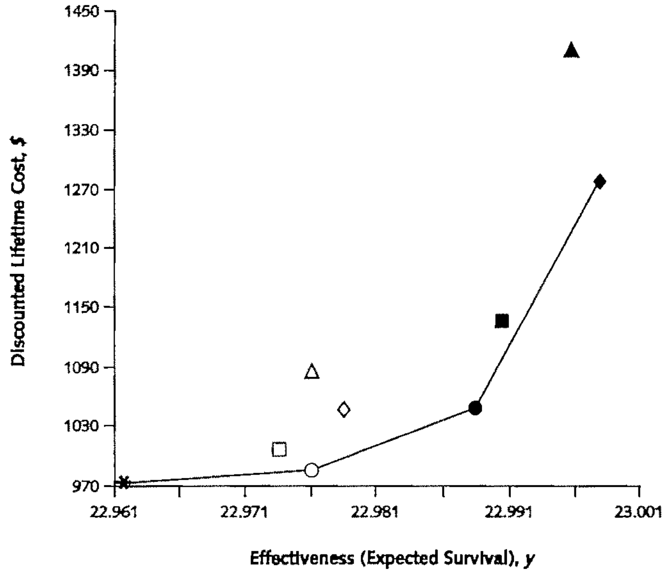
For the analyses, we used the following software: Data 3.5 and Data 4.0 Pro Beta, version 6 (Treeage Software, Inc., Williamstown, Massachusetts); Stata 6.0 (Stata Corp., College Station, Texas); and Microsoft Excel, version 5.0 (Microsoft Corp., Redmond, Washington).

RESULTS

Figure 2 shows the results of the base-case analysis. A strategy of no evaluation offered the least life expectancy. The greatest life expectancy was achieved by performing colonoscopy or barium enema plus flexible sigmoidoscopy for all patients. Colonoscopy or barium enema plus flexible sigmoidoscopy yielded an absolute increased life expectancy of 0.089 and 0.095 years, respectively, and 0.034 and 0.036 discounted years, respectively, compared with no evaluation. These strategies also yielded an increased life expectancy of 0.020 and 0.026 years (0.007 and 0.010 discounted years), respectively, compared with flexible sigmoidoscopy. All strategies incorporating anoscopy yielded greater life expectancy than no evaluation but lower life expectancy than strategies that visualized all or part of the colon. Similarly, for the base case, all strategies incorporating diagnostic visualization of the entire colon increased life expectancy compared with diagnostic strategies that visualized only part of the colon.

In one-way sensitivity analyses, the optimal strategy for maximizing life expectancy was relatively insensitive to the variables included in the model. As the probability that a neoplasm was located in the distal colon increased, the effectiveness of flexible sigmoidoscopy also increased; as the probability that a lesion is in the distal

Figure 2. **Cost-effectiveness of strategies for the evaluation of rectal bleeding in the base-case analysis.**



	Without Anoscopy			With Anoscopy		
	Symbol	Cost	Survival	Symbol	Cost	Survival
		$	y		$	y
Flexible sigmoidoscopy	●	1048	22.988	○	984	22.976
Barium enema	■	1140	22.991	□	1008	22.974
Colonoscopy	▲	1414	22.996	△	1087	22.976
Flexible sigmoidoscopy and barium enema	◆	1279	22.998	◇	1047	22.979
No evaluation	✱	972	22.962			

The figure includes the discounted lifetime cost and expected survival per patient for each of the alternative strategies examined. Incremental cost-effectiveness ratios are equal to the slope of the line between any two points and can be calculated from the data at the bottom of the figure. No evaluation offered the shortest life expectancy, and a strategy of flexible sigmoidoscopy plus barium enema offered the greatest life expectancy. All strategies using anoscopy followed by further evaluation if needed resulted in reduced life expectancy compared with all strategies in which all patients undergo evaluation of the colon with endoscopy or barium enema.

colon approached 83%, the effectiveness of flexible sigmoidoscopy became similar to that of barium enema. Moreover, the effectiveness of barium enema was similar to that of colonoscopy when the sensitivity of barium enema was equal to that of colonoscopy.

As can be computed from data in **Figure 2**, the incremental cost-effectiveness of flexible sigmoidoscopy compared with no evaluation or with any strategy incorporating anoscopy (followed by further evaluation if no anal disease was found) was less than $5300 per year of life gained. Compared with flexible sigmoidoscopy, the incremental cost-effectiveness of colonoscopy was $50 193 per year of life gained. Similarly, compared with flexible sigmoidoscopy, the incremental cost-effectiveness of flexible sigmoidoscopy plus barium enema was $23 918 per year of life gained.

Because the prevalence of colonic neoplasms increases with age, we examined the incremental cost-effectiveness ratios for persons 25, 35, and 45 years of age. As shown in **Table 3**, in an incremental cost-effectiveness comparison of each strategy relative to the next most effective strategy, incremental cost-effectiveness decreased with increasing age. For persons 25 years of age, the incremental cost-effectiveness of colonoscopy compared with flexible sigmoidoscopy was nearly $275 000 per year of life gained. In contrast, for persons 45 years of age, colonoscopy cost only $9360 per year of life gained compared with flexible sigmoidoscopy.

Our estimates were relatively insensitive to the variables in the model. In one-way sensitivity analyses comparing the strategy of flexible sigmoidoscopy with anoscopy plus flexible sigmoidoscopy (if anal disease was not identified on anoscopy), incremental cost-effectiveness increased by 50% or more only for the discount rate, the annual probabilities of progression of small and large adenomas, the probability that a neoplasm was in the distal colon, and variables that contributed to the estimated prevalence of colonic neoplasms (the prevalence of colonic neoplasms in the general population, the relative risk for neoplasms in persons with anal disease, and the relative risk for neoplasms in the persons with bleeding). In all cases, a comparison of the incremental cost-effectiveness of flexible sigmoidoscopy with that of anoscopy followed by flexible sigmoidoscopy if anal disease was not identified was less than $30 000 per year of life gained. One-way sensitivity analyses comparing flexible sigmoidoscopy to colonoscopy or to flexible sigmoidoscopy followed by barium enema if needed also demonstrated that the model was most sensitive to variables that predicted the prevalence of colonic neoplasms in persons with rectal bleeding. The highest incremental cost-effectiveness ratios were obtained when we used our lowest estimate for the prevalence of colonic neoplasms in the general population. In this case, the incremental cost-effectiveness ratio in comparisons between flexible sigmoidoscopy and colonoscopy and between flexible sigmoidoscopy and flexible sigmoidoscopy followed by barium enema if needed were $177 721 and $33 060 per year of life gained, respectively.

The comparison of a strategy of colonoscopy versus flexible sigmoidoscopy plus barium enema was sensitive to estimates of the sensitivity of these tests. When we used the maximal estimates of sensitivity of colonoscopy and the minimal estimates of sensitivity of barium enema, colonoscopy yielded the greatest life expectancy, at an incremental cost of $59 391 per year of life gained.

To further examine the variability in the model due to uncertainty surrounding the probability estimates, we performed a probabilistic sensitivity analysis. In comparing the strategy of flexible sigmoidoscopy with anoscopy followed by flexible sigmoidoscopy if needed (**Figure 3**), the mean incremental cost-effectiveness (±SD) was $11 461 ± $14 773 per year of life saved. The middle 95th percentile of this distribution of the incremental cost-effectiveness ratios ranged from flexible sigmoidoscopy yielding an increased life-expectancy at reduced cost to $52 158 per year of life gained. In a comparison of flexible sigmoidoscopy with flexible sigmoidoscopy followed by barium enema if needed, the mean incremental cost-effectiveness was $49 574 per year of life gained. The middle 95th percentile extended from $1528 per year of life to $233 667 per year of life gained.

DISCUSSION

Because of the high frequency of isolated proximal neoplasms, evaluation of the entire colon is recommended for patients older than 50 years of age with rectal bleeding (10, 11, 15, 16). Moreover, there is growing support for routine screening with colonoscopy in average-risk patients beginning at 50 years of age and earlier in patients at increased risk for colorectal cancer (1, 32, 33, 51, 53). Our study supports these recommendations by demonstrating that for patients at least 45 years of age with rectal bleeding, colonoscopy is a very cost-effective diagnostic strategy.

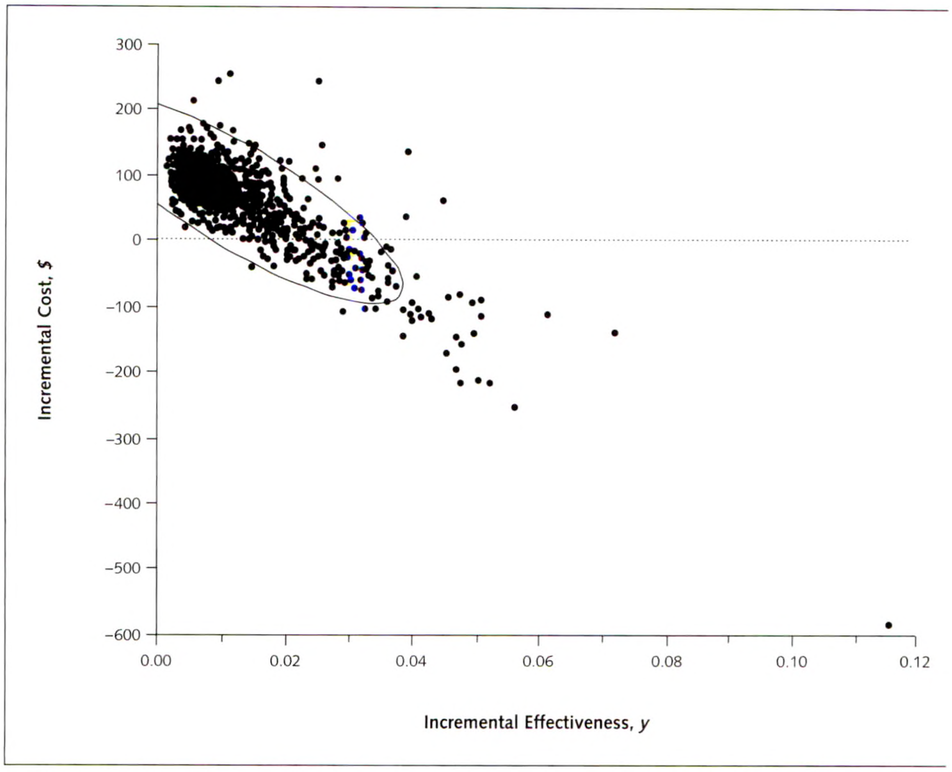
Because most young persons with bleeding do not have colonic neoplasms, physicians may believe that risks, inconvenience, and costs of diagnostic procedures outweigh potential benefits. In addition, physicians may consider an evaluation complete if anal disease is identified on anoscopy. However, the presence of anal disease does not rule out synchronous colorectal neoplasms

Table 3. **Incremental Cost-Effectiveness as a Function of Patient Age***

Incremental Cost-Effectiveness Comparison	Cost-Effectiveness according to Patient Age		
	25 y	35 y	45 y
Anoscopy followed by flexible sigmoidoscopy if needed vs. no evaluation	12 018	832	Dominant
Flexible sigmoidoscopy vs. anoscopy followed by flexible sigmoidoscopy if needed	35 187	5226	Dominant
Flexible sigmoidoscopy followed by barium enema if needed vs. flexible sigmoidoscopy	116 195	23 918	3858
Colonoscopy vs. flexible sigmoidoscopy	272 877	50 193	9360

* Dominant means that a strategy costs less and yields greater survival.

Figure 3. **Multiway probabilistic sensitivity analysis comparing flexible sigmoidoscopy in all patients with a strategy of anoscopy followed by flexible sigmoidoscopy if anal disease is not identified on anoscopy.**



The multiway analysis allowed all probability variables to vary simultaneously across the full range of values examined. The plotted values represent the incremental cost-effectiveness ratio from 1000 trials. The ellipse shows the middle 95th percentile of this distribution (from the 2.5th to the 97.5th percentiles). The mean incremental cost-effectiveness ratio (±SD) was $11 461 ± $14 773 per year of life saved. Only 2.5% of the values exceeded $52 158 per year of life gained.

(11, 28, 29). Furthermore, studies demonstrate poor ability of physicians to distinguish which patients with rectal bleeding have colonic neoplasms and which have only benign anal diseases on the basis of patient history and physical examination alone (10–12). We feel that our model includes all viable diagnostic options after routine history and physical examination, including the intermediate option of performing anoscopy as part of a routine office visit for rectal bleeding. Our model demonstrates that under almost all reasonable conditions, evaluation of the colon in young patients with rectal bleeding, regardless of the findings on anoscopy, will increase life expectancy.

Few studies have specifically addressed the cost-effectiveness of evaluating rectal bleeding. In a predominantly older population, Fine and colleagues (28) estimated that for use as an initial test, colonoscopy cost less and was safer than flexible sigmoidoscopy. In our model, the cost-effectiveness of evaluating the entire colon improved with increasing age. For patients 35 years of age or older, the cost-effectiveness of evaluation of the entire colon compared with evaluation by using flexible sigmoidoscopy was comparable to that of repeated screenings for colorectal cancer (1, 51, 54, 55). However, for 25-year-old patients, our model estimated that colonoscopy cost more than $270 000 per year of life gained compared with flexible sigmoidoscopy. Thus, in the setting of limited health care resources, some people may perceive that the incremental cost-effectiveness of evaluating the entire colon is justified only for patients 35 years of age or older.

In our model, the absolute increase in life expectancy for the entire cohort was small, measured in terms of days and weeks. As is typical of cost-effectiveness analyses (56), this seemingly small benefit reflects a large benefit in small numbers of patients who avoid dying of cancer and no measurable benefit in a large number of patients. For example, our model estimates that the prevalence of undiagnosed colorectal cancer at the time of presentation was only 1 in 11 574 patients. Despite this low prevalence of cancer at the time of bleeding, in our base-case model, a strategy of flexible sigmoidoscopy in all patients would have prevented 7.6 cases of colorectal cancer per 1000 patients over the patients' lifetime as a result of detection and removal of precancerous adenomatous polyps.

An important aspect of cost-effectiveness models is the identification of variables for which more precise estimates are needed. Our model was most sensitive to estimates of the prevalence of colonic neoplasms in patients with rectal bleeding and the rate of adenoma progression. We estimated a baseline prevalence of colonic neoplasms of 0.0432 in persons with rectal bleeding. A review of autopsy studies suggested that the prevalence of colonic neoplasms in persons 30 to 39 years of age was approximately 0.03 (26). Endoscopic studies also support our estimate (27–29). For example, Acosta and coworkers (27) found adenomatous neoplasms in 4.3% (12 of 280) of patients younger than 40 years of age with rectal bleeding or occult gastrointestinal bleeding (27). In contrast, Fine and colleagues (28) found adenomatous polyps or cancer in 19% (11 of 58) of patients younger than 40 years of age with rectal bleeding. Our assumed prevalence is therefore relatively conservative. If we have slightly overestimated the prevalence of colonic neoplasms, the magnitude of this error remains small. For example, if the true prevalence of neoplasms in the general population at 35 years of age is 0.02 instead of our estimate of 0.03, the incremental cost-effectiveness ratio comparing flexible sigmoidoscopy with no evaluation would only increase from $2864 to $6144 per year of life gained. Similarly, when comparing a strategy of flexible sigmoidoscopy plus barium enema to flexible sigmoidoscopy alone, the incremental cost-effectiveness ratio would only increase from $23 918 to $38 574 per year of life gained.

Modeling of strategies to prevent colorectal cancer requires an estimation of the natural history of benign polyps. We have assumed constant annual probabilities of transition from small to large polyps and from large polyps to locally invasive cancer. Our estimates are, again, relatively conservative compared with other models (1, 42). Our base-case model predicts that 9% and 22% of the polyps initially present will progress to invasive cancer by 10 years and 20 years, respectively. Thus, while our model appears to be sensitive to this estimate, a true transition probability lower than our base case is unlikely. Regardless, further research defining the prevalence and natural history of colonic neoplasms in this population is warranted because selection of the most cost-effective diagnostic strategy depends on these measures.

The diagnostic strategies evaluated in our model exhibit good levels of diagnostic sensitivity (1). Endoscopic tests are more sensitive at detecting small lesions than barium enema (1, 57). Most studies find barium enema or barium enema plus flexible sigmoidoscopy adequate to detect large adenomas (1, 58–60). More recently, the National Polyp Study (57) reported poor sensitivity of air-contrast barium enema, even for large polyps. The authors of that study noted that barium enema was less sensitive for adenomas in the left than in the right colon, further emphasizing the additive benefit of flexible sigmoidoscopy to barium enema. Thus, in choosing a diagnostic strategy for persons with rectal bleeding, physicians should consider the operating characteristics of the diagnostic tests as performed at a specific institution.

Our cost estimates are based on Medicare reimbursement rates and include facility fees. If procedures such as flexible sigmoidoscopy are performed without an associated facility fee, the incremental cost per year of life gained with more expensive strategies would be even greater. Similarly, in health care systems that require gastroenterology consultation before colonoscopy, flexible sigmoidoscopy or barium enema would be more cost-effective. In contrast, in health care systems that have costs lower than our estimates, the incremental cost per year of life gained would be even lower than we have calculated. We did not include the cost of initial primary care office visits because these occur before the decision model begins. However, if evaluation of the colon results in reduced rates of subsequent visits for continued bleeding, these strategies will be even more cost-effective.

Our cost estimates were somewhat lower than those used in recent cost-effectiveness models (51, 54). Use of much higher costs for sigmoidoscopy and colonoscopy, similar to those used by Frazier and cowokers (54), did not appreciably change our conclusions for persons 35 or 45 years of age. However, when costs are high, the optimal strategy for persons 25 years of age may be anoscopy followed by flexible sigmoidoscopy only if anal disease is not identified on anoscopy. Using costs similar to those used by Frazier and coworkers, we found that the incremental cost-effectiveness of anoscopy followed by flexible sigmoidoscopy (if needed) compared with no evaluation was \$21 303 per year of life gained. Performing flexible sigmoidoscopy in all 25-year-old patients instead of only patients in this age group without evidence of anal disease on anoscopy cost an additional \$59 206 per year of life gained. Thus, the most cost-effective strategy depends on patient age, the cost of the procedures, the specialist involved, and the perspective of the decision maker.

In designing the cost-effectiveness model, we elected to focus on the risk for colorectal cancer, since of the potential causes for rectal bleeding, this is the diagnosis with the greatest risk for death. We did not incorporate into our primary model all potential benefits of establishing the cause of rectal bleeding or the effect of colorectal cancer on quality of life. The quality of life of patients with colorectal cancer is generally worse than that of patients without colorectal cancer. Incorporating quality-of-life estimates would make strategies that minimize the risk for colorectal cancer appear more cost-effective. For example, in our sensitivity analyses that assumed a reduced quality of life with cancer, the incremental cost-effectiveness of evaluation with flexible sigmoidoscopy relative to no evaluation in a 35-year-old patient decreased from \$2864 to \$2734 per year of life gained. As with quality of life with colorectal cancer, had we incorporated the utility of other diagnoses (for example, colitis), evaluation of the colon would appear even more cost-effective.

Our model supports previous recommendations that persons older than 50 years of age with rectal bleeding undergo evaluation of the entire colon (10, 11, 15, 16, 28). Evaluation of younger patients with rectal bleeding can be expected to increase the average life expectancy in a cost-effective manner as well. For patients in their mid-30s and older, evaluation of the entire colon appears to yield the greatest life expectancy at an incremental cost comparable to that of other widely used screening strategies. For patients in their mid-20s and younger, flexible sigmoidoscopy alone or anoscopy followed by flexible sigmoidoscopy only in those patients without anal disease identified at anoscopy may be more cost-effective than evaluation of the entire colon. Selection of the most cost-effective diagnostic approach also depends on the sensitivity of each of the diagnostic procedures and the prevalence, distribution, and natural history of colonic neoplasms in persons with bleeding. Future research should precisely quantify the distribution and prevalence of colonic neoplasms in young patients with rectal bleeding and should evaluate the natural history of adenomatous polyps.

APPENDIX

The prevalence of colonic neoplasms in our model was calculated as follows:

$$\text{Prevalence of neoplasms} = (P_N \times (1 - P_A)) + ((RR_A \times P_N) \times P_A)$$

P_A = Prevalence of anal disease; P_N = Prevalence of neoplasms in persons without anal disease; RR_A = relative risk for colonic neoplasms in patients with rectal bleeding and anal disease compared with patients with rectal bleeding and no anal disease; $RR_A \times P_N$ = prevalence of neoplasms in patients with anal disease.

The number of cancers prevented over the lifetime of a patient cohort was estimated from the Markov model. For each cycle of the model, we determined the probability that cancer would be diagnosed in a patient. These probabilities were then summed to determine the cumulative probability of newly diagnosed cancer over an average patient's lifetime. This probability was then converted to the cumulative incidence for a cohort of 1000 patients by multiplying the probability estimate by 1000. The difference in the cumulative incidences for patients in the flexible sigmoidoscopy group and the no evaluation group represents the number of cancers prevented over the lifetime of 1000 patients by using the strategy of flexible sigmoidoscopy.

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Profiling Care Provided by Different Groups of Physicians: Effects of Patient Case-Mix (Bias) and Physician-Level Clustering on Quality Assessment Results

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Background: Patient characteristics (case-mix bias) and physician-level variation (clustering) are often overlooked in profiling the quality of care provided by different groups of physicians, such as specialties.

Objective: To examine the effect of case-mix bias and physician-level clustering on differences in quality of diabetes care between specialty groups participating in the American Diabetes Association's Provider Recognition Program.

Design: Retrospective record review of both process and outcome measures over 1 year and a cross-sectional patient survey. The sample included 29 solo and group practice sites in diverse regions of the United States. Of the 29 sites, 15 were endocrinology sites and 14 were primary care sites.

Patients: 1750 adults with diabetes.

Measurements: Process measures included frequency of hemoglobin A_{1c}, lipid, and urine protein testing; blood pressure measurement; and foot and eye examinations. Outcome measures included A_{1c} level, blood pressure, lipid levels, and patient satisfaction. Patient case-mix variables included age, sex, health status, level of education, ethnic minority status, and duration of diabetes.

Results: Unadjusted differences between endocrinologists and generalists were statistically significant for most process and outcome measures. Inclusion of patient case-mix variables reduced the statistical significance of specialty differences for some quality measures. After accounting for the substantial physician-level clustering, observed differences between specialties were no longer statistically significant for any of the quality measures except patient satisfaction.

Conclusions: The findings underscore the importance of designing physician profiling studies with sufficient power to account for physician-level variation (clustering) as well as patient case-mix. Studies that are not designed with both sufficient numbers of physicians and patients per physician may distort differences in quality of care between physician groups.

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For a glossary of terms, see end of text.
See editorial comment on pp 153-154.

Identification of physician characteristics associated with optimal management of chronic disease could serve as the basis for designing quality improvement initiatives. However, assessment of the quality of care provided by physicians with different characteristics (for example, generalists vs. specialists, male vs. female, or those in health maintenance organizations vs. those with fee-for-service arrangements) presents a unique set of methodologic problems that stem from the nature of outpatient medicine. First, if older or sicker patients with multiple diseases have different needs for health care services and different health outcomes independent of the quality of care they receive, physicians who see such patients may appear to provide lower quality of care than do those who see younger patients with less comorbid disease. Accounting for these patient characteristics (that is, avoiding case-mix bias) is therefore an essential feature of fair and accurate comparisons of physicians' quality of care.

Second, patients with specific characteristics (such as age, sex, or health problems) choose and remain with physicians who have specific characteristics (such as age, sex, specialty training, proximity, or practice style). Patients in a physician's practice (or even those seen by a small group of physicians practicing together) might therefore "cluster," that is, be more like each other and differ from patients who are drawn to another physician's practice. Thus, patients are not independent observations, as assumed by standard statistical techniques. While also inherent in any unit or "cluster" being compared (such as a health plan, a hospital, or a state), the smaller and more homogenous the unit (for example, the individual physician's office practice as opposed to a hospital), the greater the potential for a clustering problem (1). Accounting for physician-level clustering is therefore another key feature of scientifically sound profiling of physicians' quality of care.

Finally, to be reliable for profiling at the physician

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level, quality-of-care measures must be chosen that register the physician's style, or "thumbprint." For example, measures of the process of medical care (such as test ordering or interpersonal behavior) are more directly under the physician's control and are therefore more likely than some outcome and utilization measures to register the physician's thumbprint (1, 2). To detect physician style reliably, a sufficient number of patients per physician must be sampled.

Although these methodologic issues have been recognized in the design and analysis of randomized trials (1, 3, 4), attempts to address both patient case-mix and physician-level clustering in observational studies of quality-of-care assessment have been limited (2, 5–12). As part of a continuing effort to draw attention to quality of care, the American Diabetes Association (ADA) developed the Provider Recognition Program to acknowledge physicians who provide high-quality diabetes care. To illustrate the effects of patient characteristics and physician-level clustering on quality assessment results among patients with diabetes, we used ADA Provider Recognition Program data to compare two groups of physicians, in this case generalists and specialists, whose results were expected to differ (7, 13).

METHODS

Definitions

"Groups of physicians" refers to physicians who share a characteristic, such as specialty; it does not designate a collection of physicians practicing together. "Site" or "practice" refers to the office setting, as in "solo or group practice" or "endocrinologist practices," not to the behavior of physicians (as in "practice patterns"). We use a broad definition of "case-mix" that includes such patient characteristics as age, sex, level of education, and health status. "Physician-level clustering" refers to the variation in any measurements (patient characteristics or quality-of-care measures) associated with the physician. In this study, it reflects the extent to which rates of performance of quality measures differ between physicians within a specialty. The effect of this clustering is summarized by the inflation factor (also called "design effect" [1]), which is the ratio of estimated variances of differences between specialty groups, with and without adjustment for clustering (see Glossary).

Site Selection and Patient Sampling

A convenience sample of 15 managed care plans, 10 clinics, and 6 endocrinology practices responded to a nationwide ADA solicitation to participate in a diabetes-related quality-of-care study. Seven of the 15 managed care plans agreed to recruit physicians. All 10 clinics and all 6 of the endocrinology practices agreed to have some or all of their physicians participate. Thirty-one practice sites that included a total of 63 physicians agreed to participate in the study. Of these 31 sites, 2 dropped out because of the burden of data collection.

Each participating practice self-reported specialty of the practice. To avoid misclassification of practices, the investigators verified specialty. Physicians at each participating practice were asked to submit data only for those patients for whom they provided the principal diabetes care.

To maximize the reliability of physician-level quality measures, approximately 35 patients per site were to be sampled. All but 3 practice sites recruited 27 or more patients; the average number of patients sampled per site was 67. All patients received most of their diabetes care at the practice site. Practice sites recruited consecutive patients starting at an index date.

Data Collection

Clinical data were abstracted from medical records for all visits to participating physicians in the 12 months immediately preceding the index date. The care assessed was delivered between October 1994 and July 1996. Following detailed ADA specifications, personnel at each practice site abstracted study measures from patients' medical records. Abstraction by sites was determined to agree with expert ADA personnel by performing duplicate abstraction at two participating practices.

A survey to collect patient case-mix variables and ratings of interpersonal care was also administered at the time of recruitment. A majority of patients (69%) returned the survey by mail; the remainder (31%) completed the survey in the physician's office. The method of survey administration did not affect the variables analyzed. Completed patient surveys were obtained from 1258 (73.5%) patients. Compared with responders, nonresponders had a higher mean hemoglobin A_{1c} level (0.091 [9.1%] vs. 0.087 [8.7%]), had had diabetes for less time (10.8 vs. 14.3 years), and fewer received most of their care from an endocrinologist (68% vs. 73%).

Since clinical measures not found in the medical record were scored as not performed rather than as missing, none of these measures was imputed. Missing data from the survey exceeded 5% for only four variables. Values were imputed for single-item measures by using Hot-Deck (14); multi-item scales were imputed by using each respondent's average of completed items for those completing at least 50% of scale items. Although multiple imputation methods are available, a single imputation procedure for missing data was chosen for this project in order to focus on the issues of clustering and case-mix, apart from additional sources of variability.

Measures

A panel of experts recruited by the ADA identified process and outcome measures that together defined a comprehensive evaluation of quality of care for diabetes. These measures were lipid profile (frequency of measurement and levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), dilated eye examination (a note, report, or letter from a physician or optometrist documenting the date of the examination, or a dated photograph of the retina), foot examination (reference to a visual inspection or sensory examination of the feet), blood pressure, urinalysis or any test for urinary protein (such as 24-hour collection or dipstick protein testing), and self-monitoring of blood glucose (any mention of patient-collected blood glucose values and any mention of patient self-adjustment of diet or treatment on the basis of blood glucose results).

Glycated hemoglobin was recorded as hemoglobin A_{1c} or total glycated hemoglobin. Total glycated hemoglobin values were converted to hemoglobin A_{1c} values. For items that appeared more than once during the study year, the most recent value recorded was used.

Satisfaction with care was measured by using four well-tested survey items, rated on a five-point scale from "excellent" to "poor" (15): personal manner of the health care provider, overall diabetes care, explanation of laboratory results, and how well questions were answered. The proportion of "excellent" scores was used in the analysis. Self-reported health status was measured by using a single five-point rating scale from "excellent" to "poor." This item has been shown to reflect the summary of diabetes complications and comorbid conditions (16).

Statistical Analysis

All data were analyzed by using SAS software (17). We used univariate analysis to examine frequency distributions and variability in study measures. Derived variables from the patient survey were tested for internal consistency reliability by using the Cronbach α value; reliability coefficients exceeded 0.70 for all study measures. Characteristics of respondents and nonrespondents were compared by using t-tests for continuous variables and chi-square tests for proportional variables.

For each process and outcome measure, regression models were used to calculate estimated odds ratios and 95% CIs comparing the two specialties. Odds ratios were estimated from regression models with no adjustments, inclusion of patient case-mix only, inclusion of physician-level clustering only, and inclusion of both case-mix and physician-level clustering. Although the odds ratio may not be the optimal metric when performance rates are extremely high or low (18, 19), we used odds ratios only to illustrate the effects of patient case-mix bias and physician-level clustering on specialty comparisons. Models were adjusted for patient age, level of education, ethnic minority status, sex, duration of diabetes, treatment with insulin, and health status. Health status and education were entered as continuous variables. Crude and covariate-only adjusted estimates were obtained from logistic regression models.

Generalized estimation equations (20) were used to investigate the additional effect (beyond case-mix bias) of physician-level clustering on significance testing. This effect, summarized by the inflation factor, is derived from the covariate-adjusted model and the full model with both covariate and cluster adjustments. It reflects the proportional decrease (or increase) in sample size required to see statistically significant differences between the groups being compared given the extent of clustering of patients by physician. It can be written as $IF = 1 + (n - 1) \times p$, where IF is the inflation factor, p is the intraclass correlation coefficient, and n is the number of patients seen per physician. The intraclass correlation coefficient measures how similar patients are within practices and how different they are from patients in other practices (21). In this study, after adjust-

Table 1. **Proportion of Patients Conforming with Process and Outcome Measures, by Specialty and Unadjusted for Patient Characteristics**

Quality Measure	Patients of Endocrinologists ($n = 1250$)	Patients of Generalists ($n = 500$)	Difference (95% CI)	*P* Value
	%		*percentage points*	
Process measure*				
Hemoglobin A_{1c} measurement	90	79	11 (6 to 14)	<0.001
Lipid measurement	45	51	−6 (−11 to 0)	0.042
Urine protein measurement	58	42	16 (12 to 22)	<0.001
Blood pressure	91	92	−1 (−2 to 3)	>0.2
Eye examination	41	34	7 (2 to 12)	0.008
Foot examination	75	54	21 (16 to 26)	<0.001
Self-measurement of blood glucose	83	73	10 (6 to 15)	<0.001
Outcome				
Hemoglobin A_{1c} value < 0.10 (<10.0%)†	79	76	3 (1 to 8)	0.153
Hemoglobin A_{1c} value < 0.08 (<8.0%)	38	32	6 (1 to 12)	0.029
Total cholesterol level < 5.18 mmol/L (<200 mg/dL)	46	43	3 (−4 to 9)	>0.2
Low-density lipoprotein cholesterol level < 3.37 mmol/L (<130 mg/dL)	51	58	−7 (−14 to 0)	0.063
High-density lipoprotein cholesterol level‡	58	51	7 (0 to 14)	0.046
Triglyceride level < 2.26 mmol/L (<200 mg/dL)	68	57	11 (5 to 17)	<0.001
Blood pressure ≤ 140/90 mm Hg	58	52	6 (0 to 11)	0.037
Satisfaction with interpersonal care rated as "excellent"	38	22	16 (11 to 22)	<0.001

* Blood pressure was measured twice annually; all other process measures were obtained once annually.

† Unadjusted mean values were 0.087 (8.7%) for endocrinologists and 0.09 (9.0%) for generalists ($P < 0.05$).

‡ Specified levels were >0.91 mmol/L (>35 mg/dL) for men and >1.17 mmol/L (>45 mg/dL) for women.

ment for case-mix, the intraclass correlation coefficient indicates the consistency of the physician's behavior across patients in his or her practice. A high intraclass correlation occurs when the quality measures are similar for patients within a physician's practice and differ from those for patients in another physician's practice. An inflation factor of 1 implies no physician-level clustering (standard analytic approaches assuming independence of observations might therefore be appropriate), and those greater than 1 represent data with positive intraclass correlation. These methods allowed us to examine differences between specialists and generalists after accounting first for patient case-mix, then for physician-level clustering, and finally for both.

Role of the Funding Source

This research was supported by the American Diabetes Association, which developed and maintains the Provider Recognition Program. Data from the Provider Recognition Program were analyzed by the authors with support from the ADA. The ADA had no role in the design, conduct, and reporting of the study.

RESULTS

Patient and Practice Sample Characteristics

The 29 participating sites were located in 13 states; 14 were in urban locations, 10 in were in suburban locations, and 5 were in rural communities. There were 13 individual physician sites (solo practices) and 16 multiple physician (group practices) sites. Of the solo practitioners sampled, 6 were endocrinologists and 7 were internal medicine or family practice physicians (generalists). Of the multiple physician practices, 9 were endocrinology sites and 7 were generalist sites.

A total of 1750 adult patients participated in the study. The patients ranged in age from 18 to 92 years (mean age [±SD], 59 ± 15 years), 48% were male, 81% were white, and 32% had attended college. We did not distinguish between patients with type 1 and type 2 diabetes because the measures used to assess care were the same for both groups and diabetes type was not uniformly reported.

Relationship of Quality Measures to Physician Specialty

We first examined the relationship between physician groups (specialties) and quality measures. In a patient-level analysis unadjusted for patient characteristics, process and outcomes measures differed significantly between specialties (**Table 1**). Most process measures were performed significantly more often by endocrinologists than generalists. In addition, more patients of endocrinologists achieved specified outcome levels than did patients of generalists; however, only triglyceride level less than 2.26 mmol/L (<200 mg/dL) and patient satisfaction were statistically significant ($P < 0.01$). When the specified level of hemoglobin A_{1c} was defined as less than 0.08 (<8.0%), 38% of patients seen by endocrinologists compared with 32% of patients seen by generalists achieved this level ($P = 0.029$).

Variation in Patient Characteristics by Specialty

We next compared the characteristics of patients of endocrinologists with those of patients of generalists. Patients of endocrinologists differed significantly from patients of generalists for four of the seven patient characteristics studied (**Table 2**). Compared with patients of generalists, patients of endocrinologists were significantly younger and better educated, more had had diabetes for 15 years or longer, and more were taking insulin.

Relationship of Specialty to Quality Measures after Accounting for Patient Case-Mix and Physician-Level Clustering

Tables 3 and **4** show results of a three-stage examination of the effects of specialty on each of the quality measures in unadjusted analysis, analysis accounting for patient case-mix only, and analysis accounting for both patient case-mix and for physician-level clustering. We examined the statistical significance of odds ratios and the 95% CIs comparing the two specialties for each adjustment procedure. Odds ratios between the columns "Case-Mix Adjustment Only" and "Full Model Adjustment" in **Tables 3** and **4** are therefore similar, but the CIs in the latter column are wider. The inflation factor in **Tables 3** and **4** indicates the relative effect of physician-level clustering compared with that of case-mix adjustment only. Larger inflation factors indicate greater effects of physician-level clustering. An inflation factor of approximately 4.0 or greater, for example, indicates an approximate doubling of the CI (the square root of 4).

Although the unadjusted comparisons of specialties for each process measure were similar to the results shown in Table 1, the differences between specialties in the performance of annual lipid tests, eye examinations, and self-monitoring of blood glucose were no longer statistically significant after adjustment for patient characteristics (**Table 3**).

Accounting for physician-level clustering increased the variance associated with the specialty variable, such that no difference between specialties in process measures remained statistically significant (**Table 3**). The inflation factor exceeded 3.0 in all cases, suggesting that adjustment for clustering at the physician level substantially reduced the effective sample size and therefore reduced the study's statistical power to detect specialty differences in quality measures. The observed intraclass correlations for process measures, a reflection of the physician-level clustering, were moderately high compared with those in the literature (2, 22). The intraclass correlation coefficient for the hemoglobin A_{1c} process measure, for example, was 0.18; adjustment for patient case-mix did not change this value.

The **Figure** shows the variability in the proportion

Table 2. **Comparisons of Patient Characteristics (Case-Mix) by Specialty Group**

Characteristic	Patients of Endocrinolog sts ($n = 1250$)	Patients of Generalists ($n = 500$)	Difference (95% CI)*	P Value†
Mean age, y	57	62	5 (4 to 6)	<0.001
Men, %	48	48	0 (−5 to 6)	>0.2
College or greater education, %	36	20	16 (11 to 21)	<0.001
Nonwhite ethnicity, %	23	19	4 (0 to 10)	0.070
Duration of diabetes ≥ 15 y, %	39	26	13 (8 to 19)	<0.001
Use of insulin, %	68	45	23 (18 to 29)	<0.001
Mean health status score‡	53	51	2 (0 to 6)	0.080

* Differences between percentages are expressed as percentage points.
† Comparisons of mean differences in proportions of patients with selected characteristics by practice specialty.
‡ Self-reported health status was rated on a 5-point scale from "excellent" to "poor." Scores have been transformed to range from 0 to 100. Higher scores reflect better health.

Table 3. **Odds Ratios for Process Measures, by Method of Adjustment**

Process Measure*	Odds Ratio (95% CI)†			Inflation Factor‡
	Unadjusted	Case-Mix Adjustment Only§	Full Model Adjustment‖	
Hemoglobin A$_{1c}$	2.24 (1.69–2.97)	1.94 (1.44–2.62)	1.94 (0.81–1.24)	8.73
P value	<0.001	<0.001	0.14	
Lipids	0.81 (0.66–0.99)	0.86 (0.69–1.07)	0.86 (0.50–1.49)	6.40
P value	0.04	0.18	>0.2	
Urine protein	1.96 (1.59–2.42)	1.81 (1.45–2.26)	1.81 (0.83–3.96)	12.70
P value	<0.001	<0.001	0.14	
Blood pressure	0.95 (0.65–1.38)	0.79 (0.53–1.17)	0.79 (0.30–2.04)	5.74
P value	>0.2	>0.2	>0.2	
Eye examination	1.34 (1.08–1.66)	1.23 (0.98–1.54)	1.23 (0.62–2.43)	8.98
P value	<0.01	0.08	>0.2	
Foot examination	2.52 (2.03–3.13)	2.35 (1.86–2.98)	2.35 (0.86–6.47)	18.53
P value	0.07	<0.001	0.1	
Self-measured blood glucose	1.79 (1.40–2.28)	1.16 (0.88–1.53)	1.16 (0.35–3.90)	19.43
P value	0.001	>0.2	>0.2	

* Blood pressure was measured twice annually; all other process measures were obtained once annually.
† Odds ratios > 1.0 favor endocrinologists.
‡ Inflation factor (or design effect) is the ratio of the estimated SEs of the regression coefficients for full model versus case-mix model only.
§ Adjusted for patient characteristics (case-mix bias), including age, sex, ethnicity, educational level, duration of diabetes, and health status.
‖ Adjusted for both patient characteristics (case-mix bias) and cluster effect.

of patients with unadjusted HbA$_{1c}$ values less than 0.10 (10%) for each practice site within specialty. Considerable variation was observed between physicians within each specialty.

Similar results were obtained for each of the outcome measures (**Table 4**). However, although more patients of endocrinologists had hemoglobin A$_{1c}$ values less than 0.08 (8%), more had blood pressure values less than 140/90 mm Hg, and more rated their interpersonal care as "excellent"; adjustment for patient characteristics did not change the statistical significance of differences between specialties in hemoglobin A$_{1c}$ values or satisfaction results. Borderline specialty differences in lipid values in favor of generalists were statistically significant after case-mix adjustment only. Results for other lipid measures were similar (data not shown). After case-mix adjustment, differences in patients' blood pressure that initially favored endocrinologists became statistically insignificant. Accounting for physician-level clustering increased the variance associated with specialty differences for all outcome measures except satisfaction with care, such that differences between specialties were no

Table 4. **Odds Ratios for Outcome Measures, by Method of Adjustment**

Outcome Measure	Odds Ratio (95% CI)*			Inflation Factor†
	Unadjusted	Case-Mix Adjustment Only‡	Full Model Adjustment§	
Hemoglobin A$_{1c}$ value < 0.10 (<10.0%)	1.22 (0.93–1.60)	1.32 (0.99–1.76)	1.32 (0.67–2.59)	5.51
P value	0.15	0.06	>0.2	
Hemoglobin A$_{1c}$ value < 0.08 (<8.0%)	1.31 (1.03–1.67)	1.54 (1.19–1.99)	1.54 (0.92–2.57)	3.90
P value	<0.03	<0.03	0.10	
Low-density lipoprotein cholesterol level < 3.37 mmol/L (<130 mg/dL)	0.77 (0.58–1.02)	0.69 (0.51–0.93)	0.69 (0.46–1.04)	1.34
P value	0.07	0.02	0.12	
Blood pressure ≤ 140/90 mm Hg	1.25 (1.01–1.54)	1.06 (0.85–1.33)	1.06 (0.71–1.59)	3.23
P value	<0.04	>0.2	>0.2	
Satisfaction with care	2.20 (1.64–2.96)	1.95 (1.43–2.66)	1.95 (1.14–3.33)	2.98
P value	<0.001	<0.001	0.02	

* Odds ratios > 1.0 favor endocrinologists.
† The inflation factor (or design effect) is the ratio of the estimated SEs of the regression coefficients for full model versus case-mix model only.
‡ Adjusted for patient characteristics (case-mix bias), including age, sex, ethnicity, educational level, duration of diabetes, and health status.
§ Adjusted for both patient characteristics (case-mix bias) and cluster effect.

longer statistically significant (**Table 4**). As with process measures, outcome measures had moderately high intraclass correlations (for example, 0.12 for hemoglobin A_{1c} value < 0.10 [$<10\%$]) that were not affected by case-mix adjustment.

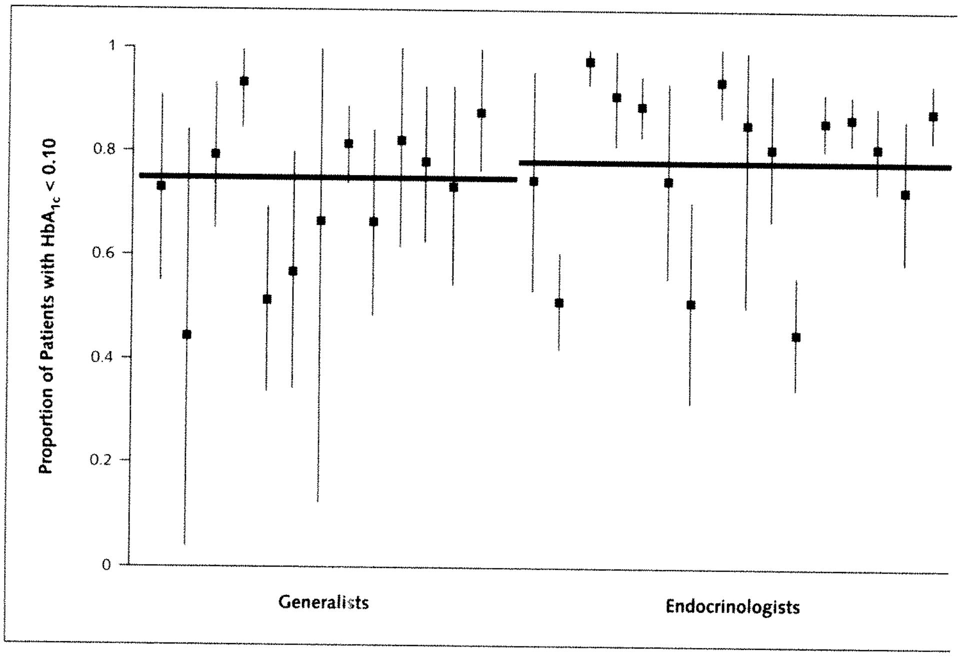
Reduction in the specification of the hemoglobin A_{1c} outcome measure from less than 0.10 ($<10\%$) to less than 0.08 ($<8\%$) reduced the inflation factor, decreased the contribution of physician clustering, and increased the contribution of patient case-mix to differences between specialties (**Table 4**).

DISCUSSION

Using data from the ADA Provider Recognition Program, we demonstrated that profiling and comparing the quality of care provided by different physician groups may be inaccurate if careful attention is not paid to patient case-mix and physician-level clustering. Although we compared generalists and specialists, our results would also apply to comparisons of quality of care provided by any group of physicians, such as those practicing in health maintenance organizations versus fee-for-service arrangements, those in higher-volume versus lower-volume practices, or older versus younger physicians. This research has implications for four areas of the design and analysis of physician-level quality-of-care studies: case-mix measurement and adjustment; choice of quality measures; sampling, power, and physician-level reliability; and analysis of physician profile data.

Patient characteristics, including age, socioeconomic status, comorbid conditions, access to health resources, and health and lifestyle behaviors, have long been understood to have a direct and independent effect on health outcomes (16, 23–32). In our study, younger, better-educated patients who had diabetes of longer duration but slightly better overall health status were more prevalent in endocrinology practices than in generalist practices. Adjustment for these patient characteristics reduced the statistical significance of specialty differences for some of the process and outcome measures. These findings are consistent with those of other recent specialty comparisons where careful adjustment for case mix was performed (6, 33–37). Because case-mix measures are imperfect, however, there may still have been

Figure. **Proportion of patients with unadjusted hemoglobin A_{1c} values less than 0.10 (10%) for each practice site within specialty.**



Squares represent the observed mean proportion of patients with hemoglobin A_{1c} values less than 0.10 ($<10\%$) seen at each site. Vertical lines represent 95% CIs. Bold horizontal lines represent the mean proportion of patients with hemoglobin A_{1c} values less than 0.10 ($<10\%$) for each specialty (76% of patients of generalists and 79% of patients of endocrinologists).

residual unmeasured case-mix differences between specialties. Improvement in these measures may improve quality-of-care comparisons between groups of physicians.

Simple adjustment for patient case-mix alone, however, could still lead to inaccurate inferences about differences in quality of care between groups of physicians. Quality measures must accurately reflect differences between the physician groups being compared and must be reliable at the physician or practice level. Our findings suggest that choosing only process or only outcome measures would have led to different conclusions about the quality of care provided by the two specialties. Specialty comparisons seldom use both process and outcome measures simultaneously (35, 38, 39), which, as our findings suggest, may be more appropriate. We also observed that choosing different thresholds for outcome measures may be important in measuring the effect of the physician versus the patient in quality-of-care assessments. As seen in **Table 4**, we observed a higher inflation factor (5.51) when the specified hemoglobin A_{1c} level was set at less than 0.10 (<10%) than when it was set at less than 0.08 (<8%) (inflation factor, 3.90). In addition, patient characteristics were more significantly associated with achievement of lower versus higher hemoglobin A_{1c} levels. Thus, higher versus lower thresholds may be a better reflection of the physician's contribution to quality of care. In future studies, comparisons of physicians' care could be improved by combining selected quality measures into multi-item scores (enhancing the reliability and validity of profile scores) and by choosing thresholds for measures that reflect physician (rather than patient) effects more accurately.

Although physicians' behavior may be highly consistent across patients in their practices, their behavior may or may not be similar to that of other physicians in their group (for example, specialty). This is the essence of physician-level clustering. We observed considerable variation between physicians within each of the specialty groups; in other words, physicians tended to behave more like individuals than like the specialty group to which they belonged. These large between-physician differences within the same specialty, coupled with the consistency of physicians' behavior across patients in their practices, increased the variance associated with specialty. Once this physician-level variation was taken into account, the specialty differences were no longer statistically significant. To see statistically significant differences between specialties given the clustering that we observed, we would have needed to increase the size of the physician sample from 3- to 20-fold, depending on the quality measure being compared.

In quality assessment, comparison of two groups of physicians (such as specialists, those scoring over or under a benchmark value, or those in different care settings) requires both a sufficient number of patients per physician to ensure physician-level reliability and a sufficient number of physicians per comparison group to account for variation with the group. Paradoxically, to obtain a reliable profile of care at the level of an individual physician or a practice, a relatively large sample of patients from that practice might be required. However, having large samples of patients per practice does not ensure optimal comparisons of groups of physicians or practices and may actually substantially increase the number of physicians or practices needed to achieve adequate power for the comparison. To compare generalists and specialists, for example, when adequate numbers of patients are sampled to obtain reliable physician- or practice-level quality-of-care scores, considerably more physicians or practices may be needed to accurately compare the specialty groups. The greater the variability in care across physicians or practices, the larger the number of physicians needed to estimate differences between physician groups, such as specialties. The Appendix shows an example of this relationship. With 1750 patients, our study was designed with 80% power to detect significant differences between physician groups in the presence of the minimal intraclass correlation coefficients that we expected on the basis of previous research (2, 22). For example, for the hemoglobin A_{1c} process measure, we had 80% power to detect an unadjusted difference of 6% between specialties. In the presence of the large inflation factor that we observed (8.7), the 11% difference between specialties in this measure was not statistically significant after adjustment for clustering. With the observed inflation factor for this measure, our study had 80% power for detecting only a larger difference (15%) between specialties. Therefore, our findings emphasize the importance of designing quality-of-care profiling studies with sufficient numbers of physicians in any comparison group to detect meaningful differences in the presence of at least moderate physician-level clustering.

Finally, our study underscores the importance of using appropriate statistical techniques to account for both patient case-mix and physician-level clustering when comparing groups of physicians. Because patients within physicians' practices are not independent observations, as assumed by many standard statistical techniques, and because physicians seem to behave more like individuals than like groups, failure to account for physician-level clustering by using an appropriate analytical method could lead to overestimation of the statistical significance of the groups being compared (1, 3, 5, 41–43). In addition to the generalized estimation equations that we used (20), other approaches also exist for analyzing cluster data (44–47).

It is assumed that some study patients might have been "co-managed" by generalists, endocrinologists, and other medical subspecialties and associate providers (for example, nurses, nutritionists, and podiatrists). We did not attempt to determine the level of co-management. We assume that such co-management would enhance patient care through the application of the experience, knowledge, and skills of multiple providers. However, to the extent that extensive co-management occurred, the unadjusted differences between specialties would have been less than those we observed.

Our study has at least two potential limitations. First, participating physicians volunteered, and patients were not randomly sampled within practices. These physicians may overrepresent those who were confident that they were providing high-quality care. Any bias introduced by sampling these practices might therefore result in higher performance on quality measures than would be expected in a more representative sample. However, even among these physicians, the variation between physicians in each specialty was unexpectedly large. Therefore, a broader sample of both physician groups would be unlikely to decrease the variation between physicians and therefore unlikely to yield findings different from those observed.

In addition, although medical record data are commonly assumed to be the "gold standard" for quality assessment, they may not be the optimal data source for this purpose. Physicians tend to record only positive findings and not document clinical care yielding negative findings. To affect our results, however, specialties would have had to differ in recording practices. A recent study suggests that specialties do not differ in this way (48).

In summary, most national quality-of-care initiatives fail to adjust adequately for patient characteristics and none adjust for variations between individual physicians or practices. The failure to take both of these important design and analytical features into account might lead to inaccurate conclusions in comparisons of profiles of quality of care provided by different groups of physicians.

GLOSSARY

Case-mix adjustment: Statistical methods applied to physician comparisons to account for case-mix bias.

Case-mix bias: The nonrandom tendency of patients with certain characteristics (such as age, comorbid conditions, or severity of illness) that affect outcomes to choose physicians with certain characteristics (such as specialty). Ignoring this tendency in comparisons of physicians would introduce bias in those comparisons.

Hierarchical modeling: Statistical technique of accounting for nested data structures (for example, patients within physician). It does not assume independence of observations, accounts for multiple levels of sources of variability measured at different levels of the hierarchy, and allows estimation of random and fixed effects.

Inflation factor: The proportional increase (or decrease) in sample size, reflecting the variation around the group mean or rate for a measure due to differences between individuals in the groups, needed for observed differences between groups to reach statistical significance.

Intraclass correlation: With respect to physician profiling, a reflection of the consistency of the physician's behavior across patients (especially if adjusted for patient case-mix) and practices.

Physician-level clustering: The nonrandom clustering of patients with certain characteristics within a physician's practice; the variation between physicians in quality measures which, after case-mix adjustment, are attributable to differences in physicians' behavior.

Physician-level reliability: Reproducibility of a physician's quality measure (rate of a desired process or outcome) across multiple samples of patients in his or her practice.

Validity: The accuracy (or absence of bias) of measurement; the extent to which a measure actually measures what it is intended to measure. (Validity of the physician profile scores is not addressed in this paper.)

APPENDIX

Following is an example of the relationship among design effects, patient and physician sample sizes, intraclass correlation coefficients, and effective sample sizes to detect differences between physician groups.

Suppose a fully randomized trial comparing two groups of

250 patients each had 80% power to detect a difference in the performance of a quality measure of 20% versus 31% (odds ratio, 1.8) for each of two physician groups, and patients were sampled with attention to the physician's practice from which they were drawn. If instead 20 physicians were sampled and then 25 patients of each physician were sampled (for the same total of 250 patients in each comparison group), the actual power of the study would depend on the intraclass correlation. Both the intraclass correlation and the number of observations in each cluster have implications for the inflation factor and the effective sample size. For example, with a very high intraclass correlation of 0.25, this nested design would have an inflation factor of 7.0 and have only 80% power to detect a much larger difference in the performance of the quality measure (20% vs. 52% [odds ratio, 4.2]) for the two physician groups. With the high intraclass correlation, each patient's response provides less independent information. Thus, adding more patients per physician only marginally increases the study's power. In the hypothetical extreme case of an intraclass correlation of 1.00, the effective sample size for this study would be 20, the number of participating physicians.

Even low intraclass correlation can significantly affect the inflation factor and, thus, the study's power. For example, in the above design, an intraclass correlation of 0.05 would produce an inflation factor of 2.2, resulting in an effective sample size of 227. This study would then have 80% power to detect a difference in the performance of the quality measure of 20% versus 37% (odds ratio, 2.4) for the two physician groups. Therefore, studies must have a sufficient number of patients seen by each physician to estimate physician performance reliably, and to make appropriate case-mix adjustments, and they must have adequate numbers of physicians to have sufficient power to detect relevant differences between physician groups.

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Reporting on Statistical Methods To Adjust for Confounding: A Cross-Sectional Survey

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Background: **The use of complex statistical models to adjust for confounding is common in medical research.**

Objective: **To determine the frequency and adequacy of adjustment for confounding in medical articles.**

Design: **Cross-sectional survey.**

Setting: **34 scientific medical journals with a high impact factor.**

Measurements: **Frequency of reporting on methods used to adjust for confounding in 537 original research articles published in January 1998.**

Results: **Of the 537 articles, 169 specified that adjustment for confounding was used. In 1 paper in 10, it was unclear which statistical method was used or for which variables adjustment was made. In 45% of papers, it was not clear how multicategory or continuous variables were treated in the analysis. Inadequate reporting was less frequent if an author was affiliated with a department of statistics, epidemiology, or public health and if articles were published in journals with a high impact factor.**

Conclusions: **Details of methods used to adjust for confounding are frequently not reported in original research articles.**

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Discovering the determinants of disease is often not straightforward, particularly if the disease or the risk factor is rare or not easily recognized (1). In case–control, cohort, and other nonrandomized studies, the groups being compared are likely to vary with respect to several demographic, clinical, and other characteristics. In randomized trials, authors often try to demonstrate that the observed treatment effect is not explained by some difference in baseline characteristics (2). The definition of confounding is that there are alternative explanations for an observed association between a risk factor and a health outcome. This may occur when one or more of these demographic or clinical characteristics are associated with one another and with the outcome of interest (3). Social class, for example, is known to be associated with cardiovascular risk factors, such as smoking, serum cholesterol level, and leisure physical activity, as well as with mortality. This difference in demographic and clinical characteristics may account for about half of the excess coronary and all-cause mortality in blue-collar workers compared with white-collar workers (4).

If confounding cannot be avoided at the design stage of a study, disentangling the web of causation is often difficult, and more or less complex statistical methods are needed. Readers of published scientific articles need to know whether and how the authors appropriately adjusted for confounding (5).

In this cross-sectional study, we sought to determine how frequently adjustment is reported in medical scientific articles and whether reporting is sufficiently detailed.

METHODS

Journal Selection

Scientific medical journals were included if they were published in English, were available in the British Medical Association's library, and had an impact factor (6) that placed it in the highest 20% of journals within its medical specialty. We excluded review journals and journals specializing in statistics, epidemiology, and public health.

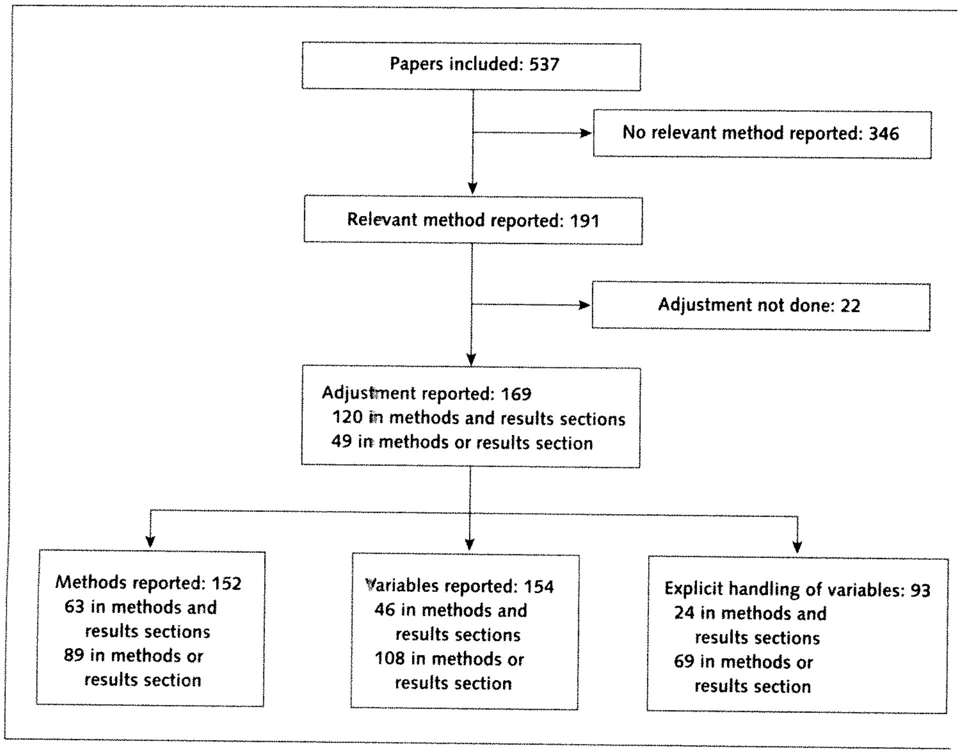
Article Selection

Two of the authors independently assessed all January 1998 issues of the selected journals to identify full-length original research articles. Short reports, scientific letters, case reports, and review articles, and animal studies were excluded.

Data Collection

We assessed whether adjustment for baseline variables or confounding was performed and whether the paper specified which method was used, the variables for which adjustment was made, and how these variables

Figure. **Articles assessed for reporting of adjustment for confounding or baseline differences and whether adjustment was reported in the methods or results section.**


Papers included: 537
No relevant method reported: 346
Relevant method reported: 191
Adjustment not done: 22
Adjustment reported: 169
120 in methods and results sections
49 in methods or results section
Methods reported: 152
63 in methods and results sections
89 in methods or results section
Variables reported: 154
46 in methods and results sections
108 in methods or results section
Explicit handling of variables: 93
24 in methods and results sections
69 in methods or results section

were handled in the analysis (that is, whether it was specified how continuous and multicategory variables were entered into the statistical model). Inappropriate reporting was defined as not reporting or insufficiently reporting on one or more of these points. For simplicity, we assumed that all multiple regression analyses were done to adjust for confounders, even though in some cases they were done to identify prognostic variables. Each paper was independently assessed by two of the authors. Agreement between the two authors was good to very good ($\kappa = 0.61$ to 0.96). Disagreement was usually caused by oversight rather than differing opinions. In case of disagreement or uncertainty, the third author (a senior statistician) was consulted.

Statistical Analysis

The univariate association between inappropriate reporting and several variables—for example, impact factor (quartiles); at least one of the authors being affiliated with department of statistics, epidemiology, or public health; and number of authors (1 or 2, 3 to 5, 6 to 10, or >10)—was assessed by using chi-square tests or chi-square tests for trend. We used multiple logistic regression to investigate simultaneously variables that showed an association with inappropriate reporting. Data were processed by using Excel 97 software (Microsoft Corp., Redmond, Washington) and Stata, release 6 (Stata Corp., College Station, Texas).

RESULTS

Thirty-four journals met our inclusion criteria (Appendix). The median impact factor of these journals in 1996 was 4.26 (interquartile range, 2.64 to 5.74). We identified 537 articles that fulfilled our inclusion criteria (**Figure**), of which 169 (32%) reported adjustment for confounding or baseline differences.

Reporting of Methods

Of the 169 articles, 152 (90%) appropriately reported methods to adjust for confounding (**Figure**), 7 reported no method, and 10 mentioned but did not

Table. **Association between Inadequate Reporting of Adjustment for Confounders and Study Characteristics in 169 Original Research Articles**

Characteristic	Studies with Inadequate Reporting, *n/n* (%)	Relative Risk (95% CI)	*P* Value*
At least one author affiliated with department of statistics, epidemiology, or public health			
No	59/105 (56)	1.00 (referent)	
Yes	17/64 (27)	0.47 (0.30–0.73)	<0.001
Number of authors			
1–2	4/8 (50)	1.00 (referent)	
3–5	28/64 (44)	0.88 (0.42–1.85)	
6–10	37/83 (45)	0.89 (0.43–1.86)	>0.2
>10	7/14 (50)	1.00 (0.42–2.38)	
Impact factor (quartiles)			
≤3.34	25/45 (56)	1.00 (referent)	
3.35–4.67	22/47 (47)	0.84 (0.56–1.26)	
4.68–9.28	21/40 (53)	0.95 (0.64–1.40)	0.008
>9.28	8/37 (22)	0.39 (0.20–0.76)	

* Chi-square test for comparing two proportions or test for trend.

adequately specify a method. In these 10 articles, the authors used the phrases "multiple regression" or "multivariable analysis."

Of articles that specified the method, multiple logistic regression analysis was the most frequently used (n = 76), followed by multiple Cox proportional hazards models (n = 43); multiple linear regression (n = 33); and other methods (n = 31), including stratified analysis, partial correlation, direct and indirect standardization, mixed-effect modeling, and age-adjusted z-score. Some papers included more than one method of adjusted analysis, but each paper was counted only once in the following analyses.

Reporting of Variables

Of the 169 articles that reported adjustment for confounding, 154 (91%) clearly specified variables for which adjustment was made, and 93 (55%) clearly stated how variables were handled (**Figure**). Only 93 articles (55%) met criteria for appropriate reporting: 51 articles had one inadequacy, 17 articles had two inadequacies, and 8 articles had three inadequacies.

Examples of Inappropriate Reporting

Example 1

A randomized, controlled trial investigated whether surfactant administered to preterm infants reduces the incidence of severe complications. The authors provided great detail to demonstrate that treatment and control groups were comparable at baseline. In a table, the authors report "baseline adjusted incidence of pulmonary complications." However, the reader is not told why adjustment was needed to present a main end point, how this adjustment was performed, or which of the 14 or more baseline variables were included (7).

Example 2

A randomized, controlled trial compared two antibiotics for the treatment of gonorrhea. The authors stated that "After correction for baseline abnormalities there was no significant difference in laboratory abnormalities." However, they did not indicate which baseline abnormalities were meant and how this correction was performed (8).

Example 3

A randomized, controlled trial compared balsalazide with mesalamine in patients with acute ulcerative colitis. The authors stated that "Logistic regression techniques were used to identify prognostic factors significantly associated with remission." The reader is told which variables were finally significantly associated with the outcome but not which variables were entered into the model (9).

Example 4

Breathing patterns and respiratory muscle performance measures during weaning were examined in a case series of 17 patients receiving prolonged mechanical ventilation. In the methods section, the authors state that "adjusted means were calculated for the variables presenting a group effect," but the reader is not told how or where this calculation was performed (10).

Determinants of Inappropriate Reporting

In 64 of the 169 articles (38%), at least one author was a methodologist (that is, he or she was affiliated with a department of statistics, epidemiology, or public health). Among papers with a methodologist-author, the rate of any inappropriate reporting was about half that of papers without a methodologist-author (Table). The rate of inappropriate reporting tended to decrease as the journal impact factor increased, but this effect was largely due to a lower rate of inappropriate reporting in the journals in the highest quartile of impact factor. The number of authors was not associated with inadequate reporting.

A multiple logistic regression model with any inappropriate reporting as the dependent variable and methodologist-author and impact factor (quartiles) as predictor variables showed that these two effects were largely independent (results not shown). Among the journals in the lower three quartiles of impact factor, 12 of 42 (29%) articles with a methodologist-author and 56 of 90 (62%) without a methodologist-author had inappropriate reporting. In contrast, among the journals in the top quartile of impact factor, the rate of inappropriate reporting was similar among articles with and without a methodologist-author (3 of 15 [20%] articles vs. 5 of 22 [23%] articles, respectively). However, because the number of papers was small and this split by impact factor was not prespecified, *P* values are not presented.

DISCUSSION

Statistical methods are often misused, and poorly presenting them leaves the reader unable to critically interpret the findings of an original research study (11, 12). Some studies use a selection procedure to reduce the number of variables for which adjustment is needed to those that are statistically significant. In such cases, authors should report all variables considered in addition to those for which adjustment was actually made.

Not reporting whether variables are treated as continuous or as categorical data may make a difference in the interpretation of the results. Transformation to fulfill the assumption of a normal distribution may or may not have been performed (13). Likewise, for categorical variables, the definition and number of categories are needed. Assuming a linear association when it is nonlinear may mask an association (14), having too few and broad categories may lead to considerable residual confounding, and having too many categories may reduce the power of a model (15, 16).

The reasons for these shortcomings may be manifold. It is possible that all the necessary information was present before peer review and was omitted during the publication process. However, errors and omissions are more likely the consequence of a system failure at many levels (17), including that of the authors, reviewers, statisticians, and editors (18).

Although data analysis may be correct despite inappropriate reporting, such reporting leaves readers unable to assess whether the data were processed appropriately. Having a methodologist as an author seems to have a "protective" effect, which is in accordance with the findings of an earlier study (15). Why articles published in journals with a very high impact factor have a lower rate of inappropriate reporting remains a matter of speculation. It may relate to the fact that these journals more frequently use statistical reviewers than do lower-ranking journals (19).

We suggest that readers, authors, referees, and editors try to assess whether original articles state which statistical method was used to adjust for confounders, for which variables adjustment was performed, and the way in which the variables were handled in the analysis.

APPENDIX

The following journals were included in the study: *American Journal of Cardiology, American Journal of Medicine, American Journal of Obstetrics and Gynecology, Anaesthesia, Anesthesiology, Annals of Internal Medicine, Archives of Dermatology, Archives of Internal Medicine, BMJ, Blood, Brain, British Journal of Anaesthesia, British Journal of Cancer, British Journal of Dermatology, British Journal of Obstetrics and Gynaecology, British Journal of Surgery, Circulation, Critical Care Medicine, Gastroenterology, Gut, JAMA, Journal of the American College of Cardiology, Journal of Gerontology, Journal of the National Cancer Institute, Journal of Pediatrics, Journal of Rheumatology, Kidney International, The Lancet, New England Journal of Medicine, Neurology, Pediatrics, Thorax, Thrombosis and Haemostasis,* and *Transplantation.*

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Health Decision Aids To Facilitate Shared Decision Making in Office Practice

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For medical decisions with more than one reasonable option, patient participation in decision making is often necessary to optimally match management decisions with patient preferences. Health decision aids are designed to facilitate shared decision making by helping patients and their physicians choose among reasonable clinical options. Although these aids vary in content, common denominators are the presentation of more than one reasonable strategy for a clinical management question and a description of the possible outcomes of the various options. Although the number of published randomized trials assessing the impact of health decision aids on the quality of medical decisions is limited (but growing), various types of decision aids do generally appear to inform patients about their treatment options better than "usual care" can. Little evidence is available to determine whether one type of decision aid is optimal, but more complicated programs seem to have larger effects. The cost-effectiveness of decision aids has not been studied, although it is enticing to think that the pattern of more conservative decisions by users of some decision aids could reduce medical care costs in a manner that is dictated by patient preferences.

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In the day-to-day practice of medicine, patients and their physicians face an increasing number of complex choices regarding prevention, diagnosis, and treatment. The options usually have different profiles of potential benefits and risks (not to mention costs). Deber and colleagues (1, 2) have thoughtfully distinguished "problem solving" tasks in medicine, which involve one "right" course of action and provide little room for patient involvement, and "decision-making" tasks, in which there are several reasonable courses of action and patient involvement is important (1, 2). The optimal choice for a decision-making task depends not only on the probabilities of various outcomes with each strategy but also on the patient's relative preferences for the possible outcome states (and their timing) and his or her attitudes toward risk (3, 4).

HEALTH DECISION AIDS

Health decision aids are designed to facilitate shared decision making by helping patients and their physicians choose among reasonable clinical options (5, 6). Although these aids vary widely in content, common denominators are the presentation of more than one reasonable strategy for a clinical management question and a description of the possible outcomes of the various options. Other components may include some form of vicarious experience with possible outcomes (through written or videotaped testimonies from former patients) or exercises designed to help clarify patients' values as they pertain to the decision at hand. More complicated, interactive decision aids allow patients to take an active part in determining the amount and type of the information they receive about their health problem. In general, decision aids are meant to supplement, not replace, the traditional process of patient counseling by clinicians.

Although decision aids generally present a menu of standard management options, they have also been used to present the additional option of a randomized clinical trial for informed patients who are at personal equipoise regarding two treatment options (7, 8).

Health decision aids take many forms. The most common are combinations of written and oral information (including audiotapes); personal counseling, sometimes supplemented by decision boards; linear videotapes; and interactive, computer-driven multimedia programs. Randomized trials have examined the effectiveness of each of these types of decision aids, addressing a variety of medical decisions. Of interest, although simple written brochures are probably the most widely used decision aids in office practice, they are the least well studied.

MEASURING A GOOD DECISION

Later in this paper I discuss the evidence on the impact of health decision aids. First, however, it is important to be clear about how one would expect such programs to affect patients and the process and outcomes of medical decision making. Several recent reviews have addressed this topic (9, 10). In the "big pic-

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ture," use of health decision aids should result in "better decisions." But how does one measure a good decision? Commonly measured outcomes in trials of decision aids include patients' knowledge about the condition of interest and its management options, their satisfaction with the process of decision making or the decision, their perceived level of participation in the decision-making process, their level of conflict about the decision, the treatment choice actually selected, and overall or disease-specific health status.

If the choice of a screening or treatment strategy is to be truly "informed," patient knowledge about the decision seems a straightforward outcome measure. Investigators studying the impact of decision aids have usually used short, problem-specific questionnaires to assess the impact of decision aids on patient knowledge. Satisfaction with the decision-making process and the decision itself can be measured by using validated instruments (11, 12). Participation in decision making is commonly assessed by using a single-item (13) or multi-item scale (14), the Autonomy Preference Index (14). The degree of conflict a patient feels about a decision is often measured by using the Decisional Conflict Scale (5). Choice of treatment is also decision specific, but changes in what patients elect to do alone do not indicate whether the therapeutic choices are "better" with a decision aid. Another logical end point for choice of strategy is whether decision aids result in selections that are more consistent with a patient's assessed outcome preferences, risk attitudes, and time preferences.

Finally, improved decision making may lead to better health status in some situations, which can be measured by using a host of disease-specific or generic health status measurements. Of note, older research with coaching interventions used to encourage patient participation at their office visits has suggested that increasing patients' participation in their care appears to improve health status, independent of effects on their diseases (15, 16). More recently, we found similar results in a trial of a decision aid for men facing a decision about treatment for benign prostatic hyperplasia (12).

There is no clear consensus on which combination of these measures best assesses the impact of a decision aid. Other attributes, such as level of patient anxiety and trust in the physician, may be important as well. I believe that measurements of knowledge, satisfaction with the decision-making process, choice of management strategy, and decisional conflict form a core set of outcome measures for trials of health decision aids. Ideally, trials should also assess patients' preferences for the important outcomes of the candidate strategies (and perhaps risk attitudes and time preferences as well) to determine whether exposure to the decision aid indeed better tailors management choices to patient preferences.

THE THORNY ISSUE OF BALANCE

When patients face medical decisions with multiple options, there may be many stakeholders. Manufacturers of screening tests, pharmaceutical agents, and medical devices may have a financial interest in promoting a particular choice, as may different specialty groups. Financial conflicts aside, different parties may strongly feel that one particular course of action is "right." Recent debates about the value of screening mammography for women in their 40s (17–19) or the value of prostate-specific antigen (PSA) screening (20–23) demonstrate these passions in action. Obviously, decision aids should be developed to present the risks and benefits of candidate options in a nonbiased way; but bias, like beauty, is in the eye of the beholder. Avoiding real or apparent financial conflicts of interest in the development of decision aids and obtaining assessments of balance from viewers (patients and physicians without an obvious stake in the management decision) are two approaches for minimizing bias while developing decision aids. However, ratings of balance by viewers can be tricky. For example, my colleagues and I have shown that although men with benign prostatic hyperplasia rated a decision aid balanced overall, men leaning toward surgery rated the program as being somewhat more supportive of surgery whereas men leaning toward nonsurgical treatment rated the program as being somewhat more supportive of avoiding surgery (24).

EFFECTIVENESS OF HEALTH DECISION AIDS

Two recent systematic reviews have described the results of studies of health decision aids. O'Connor and colleagues (25) conducted a Cochrane systematic review of randomized trials of health decision aids, while Molenaar and colleagues (26) examined both noncontrolled and controlled studies (26).

O'Connor and colleagues' review covered trials published through early 1998. Only randomized, controlled trials comparing decision aids to controls or alternative

Table 1. **Effect of Decision Aids on Patients' Knowledge of Options and Outcomes***

Decision (Reference)	Decision Aid		Comparison Intervention		Weight	Mean Difference (95% CI)
	Patients, *n*	Mean Knowledge Score ± SD	Patients, *n*	Mean Knowledge Score ± SD		
Compared with usual care						
Benign prostate disease (12)	104	75 ± 45	123	54 ± 45	14.1	21 (9 to 33)
Ischemic heart disease (27)	86	75 ± 17	94	62 ± 17	29.4	13 (8 to 18)
Ischemic heart disease (28)	61	83 ± 16	48	58 ± 16	26.4	25 (19 to 31)
BRCA1 gene test (29)	122	69 ± 19	164	49 ± 21.7	30.1	20 (15 to 25)
Total	373		429		100	19 (14 to 25)
Compared with less intensive decision aid						
Hormone therapy (30)	83	87 ± 11	87	84 ± 12	47.4	3 (−0.4 to 6)
Hormone therapy (31)	81	75 ± 20	84	71 ± 21	14.3	4 (−2 to 10)
Prenatal screen (32)	67	88 ± 15	88	87 ± 16	24.7	0.9 (−4 to 6)
Mastectomy (33)	30	83 ± 12	30	76 ± 14	13.5	6 (−0.3 to 13)
Total	261		289		100	3 (0.7 to 5)

* Knowledge tests for options and outcomes were specific to the decision and were scored from 0 (0% items correct) to 100 (100% items correct). Reprinted with permission from O'Connor and colleagues (25).

interventions were included. Patients had to be facing actual management decisions, and the decision aids being evaluated had to include, at a minimum, information on options and outcomes relevant to the user's health. The authors identified 17 trials addressing 11 screening or treatment decisions.

One outcome measured in 8 trials was patient knowledge about the condition of interest and its management options (Table 1). Four trials comparing a decision aid against "usual care" showed a significant improvement in patients' knowledge; the weighted mean difference in scores was 19 points (95% CI, 13 to 25 points) on a scale of 0 (none correct) to 100 (all correct). Four trials comparing a more intensive with a less intensive decision aid found a more modest (but still significant) improvement with the more complex program, with a weighted mean difference of 3 points (CI, 0.7 to 5 points). The clinical significance of a difference of this magnitude is uncertain. Decision aids also positively affected decisional conflict in 3 of 4 trials measuring that outcome, with a weighted mean difference of 0.3 (CI, 0.1 to 0.4) on a 0 to 5 scale. Only 1 of 5 studies measuring some aspect of patient satisfaction showed significant improvement with a decision aid (on satisfaction with the decision-making process), and the overall measure of effect was not statistically significant.

Fourteen trials examined the impact of a decision aid on the choice of a management strategy (Table 2). Here, the results depended on the type of decision. For major surgery, decision aids led to more conservative therapeutic choices, with 21% to 42% reductions in selection of the most invasive treatment option and an overall relative risk for choosing the most invasive option of 0.74 (CI, 0.6 to 0.9). No significant effect was seen with decision aids for circumcision, *BRCA1* gene screening, amniocentesis, or hormone replacement therapy. One study found a significant increase in hepatitis B vaccination with exposure to a decision aid. Three included trials addressing PSA screening gave conflicting results: Two trials showed a reduction in PSA testing, and one showed no impact. Finally, 3 of 3 trials showed that a significantly increased proportion of patients exposed to decision aids assumed a more active role in their health care decisions compared with patients receiving usual care, and 4 of 4 trials showed no increase in anxiety with the use of decision aids.

The search strategy for Molenaar and colleagues' review covered the literature through mid-1998. The 16 randomized trials identified by Molenaar and colleagues differed in definitions of decision aids, inclusion criteria, and search strategies. As result, 9 of these 16 trials were also included in O'Connor and colleagues' review. Molenaar and colleagues did not attempt a quantitative meta-analysis of the outcomes of the trials they identified. In general, these authors found less consistent effects among the trials they examined on the outcomes studied by O'Connor and colleagues and noted more heterogeneity in study results.

In addition, Molenaar and colleagues identified 14 noncontrolled studies of decision aids. Four of these

Table 2. **Effect of Decision Aids on Patients' Decisions***

Decision (Reference)	Decision Aid		Comparison Intervention		Weight	Relative Risk (95% CI)
	Patients	Patients Choosing Option	Patients	Patients Choosing Option		
	n	%	*n*	%		
Major surgery						
Coronary revascularization (28)	61	41	48	58	26.4	0.7 (0.5–1.0)
Coronary revascularization (27)	86	59	94	76	57.2	0.79 (0.6–1.0)
Prostatectomy (12)	104	5	123	8	6.2	0.74 (0.3–2)
Mastectomy (33)	30	24	30	42	10.1	0.58 (0.3–1.0)
Total	281		295		100	0.74 (0.6–0.9)
Circumcision of newborn boys						
Maisels et al. (34)	23	91.3	28	96.4	67.3	0.95 (0.8–1.1)
Herrera et al. (35)	56	84	47	87	32.7	1.07 (0.9–1.3)
Total	79		75		100	0.96 (0.85–1.07)
Testing for prostate-specific antigen						
Davison et al. (36)	50	48	50	38	31.1	1.26 (0.8–2)
Flood et al. (37)	103	11.7	93	22.6	21.8	0.52 (0.3–1.0)
Wolf et al. (38)	103	60.2	102	76.5	47.2	0.79 (0.6–0.9)
Total	256		245		100	0.83 (0.6–1.3)
Other screening						
BRCA1 gene test (29)	122	69.7	164	65.2	38	1.07 (0.9–1.3)
Amniocentesis (39)	441	37	431	34.1	62	1.08 (0.9–1.3)
Total	563		595		100	1.08 (0.95–1.22)
Other†						
Hepatitis B vaccination (40)	753	23.4	263	13.3		1.76 (1.3–2.5)
Dental surgery (41)	37	85	37	70.3		1.19 (0.9–1.5)
Hormone therapy‡ (31)	81	13.6	84	15.5		0.88 (0.4–1.8)

* Reprinted with permission from O'Connor and colleagues (25).
† Results were not combined because of heterogeneity in topics.
‡ Comparison between more intensive and less intensive decision aids.

studies addressed the feasibility of a variety of decision aids in clinical practice, while 10 reported positive evaluations from patients on the decision aids they used. Of interest, 3 noncontrolled studies found correlations between participants' elicited preferences for outcomes and their preferences or choices about treatment. These findings suggest matching of patient preferences with a management strategy, perhaps the most important theoretical goal of shared decision making. Unfortunately, in the absence of controls, it is impossible to conclude that decision aids actually improved the degree of correlation between preferences and choice of management.

Overall, the literature suggests that patients respond favorably to decision aids. In general, knowledge appears to be improved (sometimes substantially) with the use of decision aids, although how "high tech" decision aids need to be to accomplish this end is still an open question. Thus, decision aids can help make "informed choice" for testing or treatment a reality. In theory, better-informed choices should reduce risks for malpractice allegations against clinicians, but no study has addressed this hypothesis directly. The impact on patients' treatment choices varies and may depend on the type of decision aid, the nature of the decision, and the background rates of treatment in "usual care." Randomized trials of decision aids for major surgical interventions suggest that decision aids lead to less invasive treatment choices. Decisional conflict appears to be reduced, with no increase in anxiety, but there is little evidence of impact in other areas, including patient satisfaction and health status.

The number of well-designed, adequately powered randomized trials assessing the effectiveness of decision aids is still relatively small. Given the variety of types of decision aids and the number of clinical problems for which such interventions would seem appropriate, the low number and poor quality of published studies are especially disappointing. On the other hand, in some cases, there are more randomized trials of decision aids for a particular clinical problem than there are randomized trials comparing the outcomes of the different management strategies for these problems themselves.

CASE STUDY OF HEALTH DECISION AIDS: THE PSA SCREENING DECISION

The potential promise of decision aids for patients facing difficult, preference-driven decisions may be best appreciated by examining the results of studies of decision aids for one clinical problem. The PSA screening decision would seem an ideal issue to address with a decision aid. Randomized trials have not yet demonstrated whether early detection of prostate cancer is beneficial, ineffective, or harmful. Nevertheless, the PSA test has been available for more than a decade and is widely used for screening in the United States. Recent national guidelines on PSA screening suggest that the decision to test should be individualized on the basis of a discussion of the pros and cons of the test. Given the complexity of the decision, the amount of information that men (and their partners) think it would be helpful to have (42), the generally low level of knowledge about the advantages and disadvantages of the PSA test among men eligible to be screened (43), and limited time to discuss any one preventive intervention in primary care practice, it is perhaps not surprising that at least eight randomized trials have examined three different decision aids for PSA screening. Most of these trials were published after the end dates for the searches reported in the two overviews.

Three trials studied the impact of providing information about PSA screening in written or verbal form to men considering this test (36, 38, 44). In the first trial, patients in the intervention group assumed a significantly more active role in decision making and had lower levels of decisional conflict than controls. Levels of anxiety and the proportions of men selecting screening in the two groups did not significantly differ (36). In the second trial, the main outcome was interest in undergoing PSA screening, assessed on a five-point Likert scale. The intervention reduced interest in PSA screening by a group mean difference of 0.8 point ($P < 0.001$) (38). The last trial compared the provision of general written information about PSA screening with the provision of more specific quantitative visual information on the probability of false-positive and negative results. Knowledge and beliefs about PSA testing, as assessed by a pre- and a post-exposure test, were significantly more accurate in the intervention group (44).

More recently, results of five trials of the same linear videotape addressing the PSA screening decision have been reported (37, 45–47). The 22-minute videotape, developed by our group, includes testimonials by two physicians, one who has regular PSA testing for his own health care and another who does not. The first two trials were quasi-randomized trials of the PSA screening videotape in two settings: one among older men attending a free prostate cancer screening clinic and one among older men scheduled to visit a general medical clinic for a routine visit (37). In the first trial, men in the control group were assigned to review a videotape, funded by a drug company, that presented only the benefits of screening. In the second trial, the control group was assigned to receive "usual care"; group assignment depended on dates of clinic attendance. In both trials, assignment to the intervention group resulted in improved knowledge about prostate cancer screening. For example, the proportion of participants who answered "yes" to the question asking whether most men with an elevated PSA level do not have prostate cancer increased from 30% to 64% in the screening clinic and 14% to 72% in the general medical clinic ($P < 0.001$ for both comparisons).

Volk and colleagues randomly assigned 145 men to one of three interventions: a prostate cancer screening videotape only (the same videotape as that used in Flood and colleagues' two trials), the screening videotape plus a utility assessment exercise, or "usual care" (45, 48). Two weeks after enrollment, the number of knowledge questions answered correctly in both intervention groups together increased from a mean of 3.0 to 4.8 of 10 ($P = 0.001$), with no significant improvement in the control group. In addition, participants viewing the videotape rated the experience in many domains. In particular, 79% of viewers rated the videotape as completely balanced, while 16% thought it was slanted to favor screening and 5% thought it was slanted in favor of not screening; these findings suggest fairly good balance.

In a multicenter trial, Wilkins and colleagues (46) randomly assigned 422 men to a group that viewed the same PSA videotape before a scheduled primary care visit or to a group that received usual care. Patients assigned to the intervention group were more satisfied with the information they received, demonstrated significantly greater knowledge of PSA testing, and expressed significantly stronger preferences for active participation in making medical decisions about their health care.

Table 3. **Summary of Studies Evaluating the Effect of Decision Aids on Prostate Cancer Screening Behavior***

Source (Reference)	Participants	Type of Decision Aid	Screening Rate, % (*n per group*)		Odds Ratio (95% CI)
			Patients Receiving Decision Aid	Control Patients	
Flood et al. (37)	Unselected patients with scheduled ambulatory visits	Linear videotape†	11.7 (103)	22.6 (93)	0.45 (0.21–0.98)
Flood et al. (37)	Men presenting for free prostate-specific antigen screening	Linear videotape†	98.4 (184)	100 (188)	NA‡
Volk et al. (45, 48)	Unselected family medicine patients	Linear videotape†	34.3 (70)	59.7 (67)	0.35 (0.18–0.70)
Wilkins et al. (46)	Unselected Veterans Affairs patients recruited from outpatient clinics	Linear videotape†	54 (213)	80 (209)	0.30 (0.19–0.45)
Davison et al. (36)	Men presenting for a periodic health examination	Verbal and written discussion	28 (50)	21 (50)	1.38 (0.56–3.41)
Schapira and VanRuiswyk (44)	Veterans Affairs patients responding to a letter solicitation	Specific quantitative information	82 (122)	84 (135)	1.13 (0.59–2.16)
Frosch et al. (47)	Male patients participating in a Health Appraisal screening program	Discussion	82.2 (45)	97.7 (43)§	0.11 (0.02–0.67)
		Linear videotape†	60.0 (46)		0.04 (0.01–0.17)
		Linear videotape† and discussion	50.0 (42)		0.02 (0.01–0.10)

* Modified with permission from Volk and Spann (49). NA = not available.
† All these trials used the same linear videotape addressing the decision to have prostate-specific antigen screening.
‡ Odds ratio cannot be computed because all controls selected screening.
§ Control group was the same for all three comparisons.

Finally, Frosch and colleagues (47) most recently reported the results of a four-arm randomized trial among 176 men recruited through the Health Appraisal screening program of the Kaiser Permanente health plan. Participants were randomly assigned to usual care, a face-to-face discussion about the pros and cons of PSA testing, the same PSA videotape used in the previous trials, or a combination of the videotape and the discussion. The proportion of men selecting PSA testing was about 98% with usual care, 82% with the discussion, 60% with the videotape, and 50% with both the videotape and the discussion ($P < 0.001$).

Table 3 summarizes the impact of all the decision aids studied in these trials on participants' actual PSA screening decisions. In four of the seven trials that reported this outcome and four of the five trials of the videotape-based decision aid, the proportion of men having PSA testing significantly decreased. All six trials examining men's knowledge about PSA testing revealed large, statistically significant improvements, suggesting that the generally more conservative decisions about PSA screening in the intervention group were indeed better informed.

CHALLENGES OF IMPLEMENTING HEALTH DECISION AIDS TO FACILITATE SHARED DECISION MAKING IN PRIMARY CARE

Barriers to the use of decision aids in office-based primary care practice are both psychological and logistic. From the psychological perspective, most physicians probably think they already are doing a good job of educating patients and involving them in decision making, despite some growing evidence to the contrary (50–52). Some clinicians undoubtedly prefer a more paternalistic role and genuinely feel that such an approach is better for their patients. In fact, in a recent small survey performed as part of the implementation of two interactive health decision aids addressing choice of treatments for breast cancer and ischemic heart disease, physicians generally agreed with the statement, "Most patients prefer the doctor to take responsibility for their medical problems" (53). Moreover, a 1996 survey comparing internists' and their patients' ratings of the importance of different elements of outpatient care found that physicians rated the importance of providing health-related information considerably lower than did their patients (54).

However, logistic problems with implementing shared decision making have been a real issue, too. Making time and space available in office practice for patient education in general and use of decision aids in particular is problematic, particularly for more complex videotape- or computer-based decision aids. Coordinating mailings or in-office viewings of videotapes, as was done in many of the trials of the PSA decision aid, may be too much for small offices to take on. Hospitals or larger practices might centralize these tasks, but the process of referral can then become cumbersome and even rate-limiting (53). Finally, time spent by practice personnel in helping patients access and use decision aids often represents an extra burden and expense. As reflected in Molenaar and colleagues' review, however, patient acceptance of health decision aids does not appear to be a barrier, once the logistic difficulties in getting them together at the right place and time are overcome. Clinicians interested in a catalog of existing health decision aids for various medical conditions can access a list prepared by the Ottawa Health Decision Centre (available at www.LRI.ca/programs/ceu).

CONCLUSIONS

Health decision aids are a theoretically attractive option for informing patients about their management options and facilitating their participation in preference-driven medical decisions. Although the number of published randomized trials assessing the impact of health decision aids on the quality of medical decisions is limited (but growing), various types of decision aids generally appear successful in better informing patients about their treatment options than "usual care" does. For some, the ability of decision aids to make "informed choice" more truly informed may be sufficient to advocate their use. Moreover, exposure to decision aids for major elective surgical interventions and the PSA screening decision appears to lead to more conservative treatment choices by patients. However, the impact of decision aids on treatment choice probably depends on the setting, the decision, and the nature of the decision aid itself. Decision aids studied in randomized trials are heterogeneous in format and content; in particular, the volume of quantitative information in the programs and how that information is communicated vary considerably. Little evidence is available to determine whether one type of decision aid is "optimal," although more complicated programs in general seem to have larger effects. Relatively few trials have specifically studied potential side effects of health decision aids, including potentially heightened anxiety. The cost-effectiveness of decision aids has not been studied, although it is enticing to think that the pattern of more conservative decisions by users of some decision aids at least has the potential to reduce medical care costs in a manner that is dictated by patient preferences.

Further study of the impact of decision aids on patients and their decisions in randomized trials, including trials comparing different types of decision aids, is clearly needed (although a realist might argue that the body of evidence from randomized trials supporting the positive effects of decision aids for the PSA screening decision is already considerably more convincing than the randomized trial evidence in favor of the widely popular PSA screening test itself). Incorporating decision aids into office practice remains a formidable challenge. Major questions remain about how to avoid bias in decision aids, how much quantitative information to present and how it should be presented, and how to tailor presentations for users from different cultural and ethnic groups and with different education levels. However, all these questions are equally applicable to how clinicians themselves present information to patients about their medical decisions behind closed office doors, a process that has also been understudied.

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AD LIBITUM

Correction

Yesterday, I drove
flanked by lifeless buildings.
The road sublimated
into a pair of men
whose fates were sealed
in reflective vests
that confessed:
Department of Corrections.

As one gathered
litter, the other
inquired
through vacuous
eyes:

Given features
so akin,
where did our fates
jackknife?

And I,
built up speed
to leave
his reflection
a few miles
behind.

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2001–2002 Series: Update Sessions from ACP–ASIM's 2001 Annual Session
Margaret Ring Gillock, Editor/David A. Cramer, MD, Co-Editor/Paul T. Kefalides, MD, Co-Editor

Update in Hematology

Joseph P. Catlett, MD, and Barbara M. Alving, MD

In the past several years, there has been a veritable explosion of new and impressive treatments that not only will alter the management of leukemia and lymphoma but are expected to have far-reaching effects in general internal medicine. Target-specific drugs, including monoclonal antibodies and selective enzyme inhibitors—along with so-called designer drugs—have ushered in a new era in medicine. Examples in this Update are rituximab, a monoclonal antibody effective in non-Hodgkin lymphoma and the oral antileukemia drug STI-571. We also discuss advances in the following areas of hematology: self-management of oral anticoagulant therapy, understanding risks for venous thromboembolism in women during pregnancy and in postmenopausal women who are undergoing hormone replacement therapy, and management of patients with sickle-cell disease.

Applications of Rituximab

Rituximab Is an Effective Initial Systemic Treatment for Low-Grade Non-Hodgkin Lymphoma

Hainsworth JD, Burris HA 3rd, Morrissey LH, et al. Rituximab monoclonal antibody as initial systemic therapy for patients with low-grade non-Hodgkin lymphoma. Blood. 2000;95:3052-6. [PMID: 10807768]

Rituximab (Rituxan, Genentech, Inc., South San Francisco, California, and IDEC Pharmaceuticals Corp., San Diego, California) is a humanized murine monoclonal antibody directed against the CD20 antigen, which is expressed on B lymphocytes in more than 90% of patients with B-cell non-Hodgkin lymphoma. The binding of the antibody to CD20 antigen on malignant B cells in vitro (as well as normal B cells) results in cellular destruction through a combination of cell-mediated cytotoxicity and complement-dependent cell lysis. Rituximab also triggers programmed cell death (apoptosis), and some investigators believe that this may be the most important mechanism of in vivo cell death. Response rates have approached 50% in patients with low-grade non-Hodgkin lymphoma who are resistant to conventional chemotherapy, a population with few treatment options (1).

Hainsworth and colleagues evaluated a new patient group for rituximab: chemotherapy-naive patients. The authors infused rituximab (375 mg/m^2) once per week for 4 weeks in patients with low-grade non-Hodgkin lymphoma who had never received chemotherapy. Some of them had relapsed after spot radiation therapy. Of 39 patients completing the first 4-week course, 21 (54%) had an objective response (2 of these had a complete response). Another 14 patients had a minor response or stable disease, and only 4 (10%) had progressive disease. Three of 13 patients given a second course of treatment improved, increasing the overall response rate to 64% and the complete response rate to 15%. More than half of patients with follicular or small lymphocytic lymphoma responded. Rituximab was well tolerated; only 1 patient had serious toxicity, in the form of chest pain and ischemic electrocardiography changes. Toxicity was mainly infusion related and consisted of fever, chills, and mild nausea or vomiting occurring primarily with the first infusion. Significant myelosuppression did not occur.

Rituximab is a targeted, minimally toxic treatment that is highly effective against low-grade non-Hodgkin lymphoma in patients who have and have not received previous treatment. If needed, additional courses may be given every 6 months, which would allow time for the normal B cells to recover.

Immune Thrombocytopenia Responded Well to Rituximab in a Patient with Graft-versus-Host Disease

Ratanatharathorn V, Carson E, Reynolds C, et al. Anti-CD20 chimeric monoclonal antibody treatment of refractory immune-mediated thrombocytopenia in a patient with chronic graft-versus-host disease. Ann Intern Med. 2000;133:275-9. [PMID: 10929168]

Chronic graft-versus-host disease (GVHD) develops in roughly half of long-term survivors of bone marrow transplantation whose grafts come from HLA-identical donors (2). These patients frequently have autoantibodies to cell-surface and intracellular antigens, and one of the manifestations is immune-mediated thrombocytopenia. Ratanatharathorn and colleagues evaluated ritux-

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For author affiliations and current addresses, see end of text.

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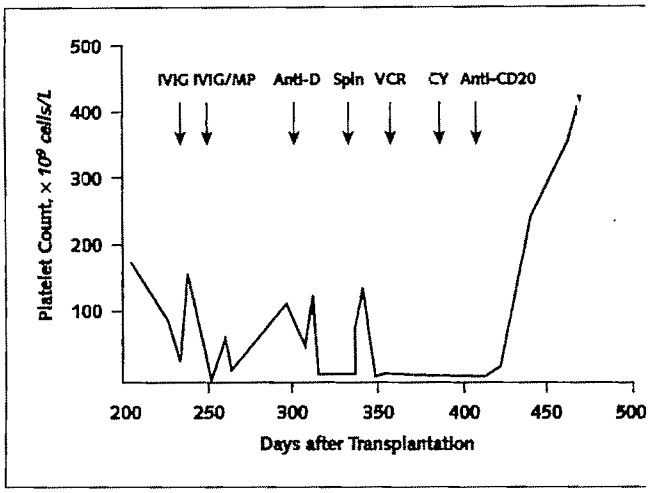
Figure. **Clinical course of a patient with chronic graft-versus-host disease in whom severe refractory immune-mediated thrombocytopenia responded to treatment with anti-CD20 monoclonal antibody.**



Anti-CD20 = rituximab; Anti-D = anti-D antibody; CY = cyclophosphamide; IVIG = intravenous immunoglobulins; MP = methylprednisolone; Spln = splenectomy; VCR = vincristine. Reproduced from Ratanatharathorn et al. Ann Intern Med. 2000;133:275-9.

imab in a 32-year-old woman who developed severe GVHD and immune thrombocytopenia after receiving an allogeneic hematopoietic stem-cell transplant for chronic myelogenous leukemia (CML). After infusion of peripheral blood stem cells from an HLA-matched sibling, the patient received methotrexate and tacrolimus but nevertheless developed acute and then chronic GVHD. Transplantation led to hematologic reconstitution, but the platelet count decreased to 28 × 10^9cells/L. The platelet count increased temporarily after treatment with methylprednisolone and mycophenolate and with anti-D immune globulin. Although the platelet count increased after laparoscopic splenectomy, it soon decreased to 2 × 10^9cells/L and did not respond to intravenous vincristine and cyclophosphamide. Finally, starting on day 404, the patient received weekly infusions of rituximab at a dose of 375 mg/m^2 over 4 weeks; this led to a sustained increase in platelet counts (**Figure**). Tacrolimus and mycophenolate were tapered and withdrawn without significant clinical evidence of chronic GVHD. Titers of platelet-associated antibody became negative within about 4 months of rituximab therapy, and platelet counts were normal at last follow-up (11 months after the start of monoclonal antibody treatment).

This experience supports the efficacy of rituximab for treating conditions that feature B-cell dysregulation, such as GVHD and immune-mediated thrombocytopenia.

Pilot Study Supports a Trial of Rituximab in Steroid-Resistant Patients with Idiopathic Thrombocytopenic Purpura

Saleh MN, Guthell J, Moore M, et al. A pilot study of anti-CD20 MoAb rituximab in patients with refractory immune thrombocytopenic purpura (ITP) [Abstract]. Blood. 2000;96:252a.

Sixteen patients with idiopathic thrombocytopenic purpura who had not responded to multiple measures (including steroids and, in 7 patients, splenectomy), completed a trial of rituximab. Of 13 patients who received a standard regimen of four weekly rituximab doses of 375 mg/m^2, 2 had a complete response and 1 had a partial response (overall response rate, 23%). Platelet counts, initially less than 75 × 10^9cells/L, increased to greater than 150 × 10^9cells/L in complete responders; a count of 100 × 10^9cells/L defined a partial response. Most experts probably would accept a platelet count of 30 × 10^9cells/L as an adequate response. Although preliminary, these results suggest that for patients with idiopathic thrombocytopenic purpura who are resistant to conventional treatments, a trial of rituximab (which is well tolerated) may help prevent serious or fatal bleeding associated with this disorder.

In a complementary study of 25 patients with chronic idiopathic thrombocytopenic purpura who had not responded to at least two and as many as five treatment regimens (including eight splenectomies), rituximab led to a response rate of 52% (3). Some patients had a complete response, with a platelet count exceeding 100 × 10^9cells/L, whereas others had a minor increase in platelet count but required no further treatment. Seven of 13 responses lasted 6 months or longer, and re-treatment succeeded in 2 patients who had relapsed. In most cases, platelet counts increased within 1 week after the first of four rituximab infusions. The one case of discontinued treatment was due to chills. No infections were reported.

Tyrosine Kinase Inhibitor Therapy for Chronic Myelogenous Leukemia

The results of two recently published studies attest to the promise of a new orally active selective tyrosine kinase inhibitor, STI-571 (Gleevec, Novartis Pharmaceuticals, Basel, Switzerland), for treating all phases of CML. The Philadelphia chromosome, which characterizes CML, results from a reciprocal translocation of the *abl* locus on chromosome 9 to the *bcr* locus on chromosome 22. The resulting oncogene, *bcr-abl*, is expressed as an oncoprotein with aberrant tyrosine kinase activity that continuously transmits proliferative signals to the cell nucleus and ultimately causes malignant transformation. STI-571, identified after screening of many tyrosine kinase inhibitors, was chemically modified to selectively block the tyrosine kinase activity of the *bcr-abl* oncogene. It is also active against other protein kinases, such as the receptor for stem-cell factor (c-kit) and platelet-derived growth factor receptor.

STI-571, a Tyrosine Kinase Inhibitor, Is Effective against Interferon-Resistant CML

Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344:1031-7. [PMID: 11287972]

This phase I dose-escalating trial evaluated the safety and efficacy of STI-571 in 83 patients with chronic-phase CML who had not responded to treatment with interferon-α. Dosages ranged from 25 to 1000 mg/d, and no maximum tolerated dose was identified. Adverse effects were grade 1 (mild) to grade 2 (moderate), even at higher dosages of 600 to 1000 mg/d; the most frequent adverse effects were nausea (43%), myalgias (41%), edema (39%), and diarrhea (25%). All but 1 of 54 patients given daily doses of at least 300 mg had a complete hematologic response, defined as a reduction in the leukocyte count to less than 10×10^9cells/L and a reduction in the platelet count to less than 450×10^9cells/L, maintained for at least 4 weeks. These complete responses occurred within the first month of treatment and have been maintained in 51 of 53 patients (median follow-up, 265 days).

Cytogenetic responses were based on the analysis of 20 cells in metaphase and were classified by the number of Philadelphia chromosome–positive cells: complete (no cells positive), partial (1% to 35% of cells positive), minor (36% to 65% of cells positive), and absent (>65% of cells positive). Twenty-nine patients had a cytogenetic response; 7 of these patients had a complete response. These responses occurred as early as 2 months and as late as 10 months after start of therapy (median time to the best cytogenetic response, 148 days). Three patients with a complete response tested negative on two highly sensitive methods for detecting the presence of disease (fluorescence in situ hybridization for 2 patients and polymerase chain reaction for 1 patient).

STI-571 Is an Effective and Relatively Safe Treatment for CML in Myeloid Blast Crisis

Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med. 2001;344:1038-42. [PMID: 11287973]

This dose-escalating pilot study evaluated STI-571 in 58 patients, 38 of whom had myeloid blast crisis of CML and 20 of whom had Philadelphia chromosome–positive acute lymphoblastic leukemia or lymphoid blast crisis of CML. Blast crisis was defined as more than 30% blasts in the peripheral blood or bone marrow. Philadelphia chromosome–positive patients with acute lymphoblastic leukemia had relapse after standard chemotherapy or were resistant to this therapy. Because the study is still in progress, the results reported represent an interim analysis of the data.

Dosages of STI-571 ranged from 300 to 1000 mg/d. The most frequent adverse effects reported included nausea, vomiting, and edema; most were grade 1 (mild) or grade 2 (moderate), as in Druker and colleagues' previous study. However, severe neutropenia and thrombocytopenia occurred in 40% and 33% of patients, respectively. Liver enzyme levels increased in 8 patients (14%); this increase was not related to dose and required discontinuation of therapy in only 1 patient. Sixteen patients died of disease progression, and no deaths were attributed to the study drug.

Forty-six patients (79%) had a 50% or greater decrease in the peripheral blast count. Overall response rates were 55% for patients with myeloid blast crisis and 70% for those with lymphoid blast crisis. Of 38 patients in myeloid blast crisis, 4 had a complete hematologic remission, defined as a lack of obvious leukemia in the marrow and a return of adequate normal hematopoiesis. Of the 20 patients with lymphoid blast crisis of CML or Philadelphia chromosome–positive acute lymphoblastic leukemia, 4 had a complete hematologic remission. Response was not related to dose. Five patients had complete cytogenetic responses: 3 patients with myeloid blast crisis and 2 with lymphoid blast crisis. The response appeared to be more durable for patients with myeloid blast crisis than for those with lymphoid blast crisis or acute lymphoblastic leukemia.

Treatment options have been limited for patients in CML blast crisis and those with Philadelphia chromosome–positive acute lymphoblastic leukemia. These preliminary findings are encouraging, even for patients who have not responded well to traditional induction chemotherapy.

Summary of Results

Patients with chronic-phase CML usually respond hematologically to STI-571, and those with accelerated or blast-phase disease have responded hematologically nearly two thirds of the time. Rates of cytogenetic response are also impressive, especially considering that patients with accelerated or blast-phase disease have had few treatment options. Most of these patients are resistant to chemotherapy, and, when they do respond, the duration is usually limited. Toxicity from STI-571 was generally mild, with severe neutropenia and thrombocytopenia mostly confined to critically ill patients in blast crisis. STI-571, conveniently administered by the oral route, is a significant advance in targeted treatment. It may well prove effective against other types of cancer that overexpress tyrosine kinase. Preliminary results in patients with gastrointestinal stromal tumors that overexpress c-kit are promising. Studies are also under way in patients with small-cell lung tumors that express this stem-cell factor receptor.

Anticoagulation

Self-Management of Oral Anticoagulation Provided Control as Good as or Better Than a Specialized Clinic

Cromheecke ME, Levi M, Colly LP, et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. Lancet. 2000;356:97-102. [PMID: 10963245]

Treatment with a vitamin K antagonist prevents thromboembolism, but careful laboratory monitoring and appropriate dose adjustments are necessary. The advent of small, portable devices has made patient self-monitoring and dose adjustment feasible. This randomized crossover trial from the Netherlands compared self-managed anticoagulation with care at a specialized anticoagulation clinic for 3-month periods. The participants, 50 patients receiving long-term oral anticoagulant therapy, had the international normalized ratio (INR) measured at 1- to 2-week intervals during both phases of the study using a capillary finger stick and an automated CoaguChek PT device (Roche Diagnostics, Indianapolis, Indiana) during the self-management phase. All patients took part in a structured educational program and had an opportunity to measure their INR under supervision and then in the home setting. The patients used a standard dose-adaptation nomogram to adjust their warfarin dose but were encouraged to tailor dosing according to their experience.

The self-monitoring and clinic management periods did not substantially differ with regard to the primary end point, the number of estimates in the therapeutic range (therapeutic target value, ± 0.5 INR unit). Patients met the primary end point during 55% and 49% of the self-monitoring and clinic management periods, respectively (odds ratio, 1.2 [95% CI, 1.0 to 1.6]). The proportion of patients within the therapeutic target range more than half the time was 60% with self-management and 52% during clinic care. The respective figures for being within range more than 75% of the time were 27% and 12% (odds ratio, 2.5 [CI, 1.0 to 6.7]). Thirty-four of 49 evaluable patients had better control during self-management (odds ratio, 4.6 [CI, 2.1 to 10.2]), although similar numbers of dose adjustments were made in the two groups. Serious deviations from the treatment goal (an INR <1.5 or >5.0) occurred during 3.5% of the self-management period and 5.3% of the clinic period. No major bleeding episodes occurred, and minor bleeding was more frequent during clinic management. Self-management was associated with higher estimates of general satisfaction with treatment and significantly lower scores for daily anxiety and distress.

Self-management of anticoagulant therapy not only is feasible—it also allows monitoring of treatment at least as well as can be done in a specialized clinic and is better appreciated by the patients themselves. Several so-called near-site devices have been approved for home use in the United States. Home monitoring holds great promise for adherent patients who can implement the procedures properly—especially those living far from a monitoring site. The patients in this study had a wide range of indications for anticoagulation, including atrial fibrillation, previous venous thromboembolism, and presence of a prosthetic heart valve. Much work remains in determining how best to maintain control of self-managed anticoagulant therapy.

Oral Vitamin K Proved Effective in Patients Who Received Overanticoagulation with Warfarin

Crowther MA, Julian J, McCarty D, et al. Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomised controlled trial. Lancet. 2000;356:1551-3. [PMID: 11075768]

Because coagulopathy is a frequent complication of warfarin therapy, this multicenter Canadian study attempted to determine whether vitamin K therapy is safe and effective, compared with placebo, for rapidly decreasing the INR to within the therapeutic range in patients who have received overanticoagulation. In this double-blind, randomized study, 92 patients receiving warfarin who had an INR between 4.5 and 10.0 but were asymptomatic had warfarin withheld and were assigned to receive 1 mg of vitamin K orally or a placebo. The trial took place at five tertiary care hospitals. The INR values increased in 9% of placebo recipients but in none of those given vitamin K ($P = 0.056$). On the day after treatment, 16% of patients given vitamin K and none of those assigned to placebo had an INR less than 1.8 ($P = 0.012$). After the second trial day, INR values were similar in the two groups. Among 75 patients who received warfarin for 1 week or longer, 58% of those given vitamin K and 17% of those given placebo had an INR within the target range of 1.8 to 3.2 the day after treatment. During 3-month follow-up, 4% of vitamin K–treated patients and 17% of those receiving placebo had bleeding episodes. Overall, significantly less bleeding occurred in the vitamin K group (odds ratio, 0.187 [CI, 0.019 to 0.999]; $P > 0.2$). The only major bleeding episode occurred 3 days after vitamin K treatment, when the patient's INR was 2.0. One patient in each group had a thrombotic episode.

This experience shows that administering low-dose vitamin K orally to patients who had received overanticoagulation with warfarin limits bleeding complications without causing an undue risk for thrombosis. Vitamin K was given in liquid form using a parenteral preparation. A 1-mg tablet for oral use will be needed if this approach becomes widely used.

A cohort study of patients receiving long-term warfarin therapy whose INR was 6.0 or higher showed the importance of controlling the INR (4). Major bleeding occurred in 4.4% of patients during a 2-week follow-up period but in no patients whose INR was within the target range. Patients who have previously received vitamin K treatment do not become resistant to warfarin when vitamin K therapy is reintroduced. Vitamin K may also help patients who are extremely sensitive to warfarin because they metabolize it very slowly; these patients require low warfarin doses and are at risk for excessive anticoagulation with warfarin when first starting treatment with a standard dose of this drug.

Thromboembolic Disease

Postmenopausal Hormone Replacement Therapy Is Related to an Increased Risk for Venous Thromboembolism

Grady D, Wenger NK, Herrington D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. Ann Intern Med. 2000;132:689-96. [PMID: 10787361]

Recent observations suggest that hormone replacement therapy (HRT) increases the risk for both deep venous thrombosis and pulmonary embolism twofold to fourfold. In an attempt to confirm or rule out such an association, Grady and colleagues analyzed data from the Heart and Estrogen/progestin Replacement Study (HERS), a randomized, double-blind, placebo-controlled trial undertaken at 20 U.S. centers. Participants were 2763 postmenopausal women younger than 80 years of age (mean age, 67 years) who had coronary disease (myocardial infarction, bypass surgery, angioplasty, or at least 50% narrowing of a major coronary artery) but no history of venous thromboembolism. None of the women had undergone hysterectomy. Active treatment in HERS consisted of 0.625 mg of conjugated equine estrogens daily plus 2.5 mg of medroxyprogesterone acetate daily.

The authors thoroughly analyzed the data after findings suggested that women assigned to HRT had an increased risk for coronary heart disease events. As a result of these findings, the HERS investigators asked all women to cease taking study medication after a mean follow-up of 3.3 years. During an average follow-up of just over 4 years, with visits every 4 months, venous thromboembolic events occurred in 34 women receiving HRT and 13 receiving placebo (relative hazard, 2.7 [CI, 1.4 to 5.0]; $P = 0.003$). The excess risk associated with HRT was 3.9 per 1000 woman-years of follow-up (CI, 1.4 to 6.4 per 1000 woman-years). The number needed to treat for harm was 256 per year (CI, 157 to 692). Individually, both deep venous thrombosis and pulmonary embolism occurred more often in women taking HRT; the relative hazard for both events was 2.8. Two women receiving HRT died of pulmonary embolism. Results were similar when analysis was limited to women who reportedly had taken more than 80% of their assigned medication. Multivariate analysis showed an increased risk for venous thromboembolism in women with lower-limb fractures (relative hazard, 18.1 [CI, 5.4 to 60.4]), those with cancer (relative hazard, 3.9 [CI, 1.6 to 9.4]), and those who had undergone inpatient surgery in the past 90 days (relative hazard, 4.9 [CI, 2.4 to 9.8]). Nonsurgical hospital admissions also were a risk factor (relative hazard, 5.7 [CI, 3.0 to 10.8]). On the other hand, thromboembolism was only half as likely in women taking aspirin (relative hazard, 0.5 [CI, 0.2 to 0.8]) or statin drugs (relative hazard, 0.5 [CI, 0.2 to 0.9]).

This analysis of data from HERS points to a twofold to threefold increase in risk for venous thromboembolism in postmenopausal women with coronary heart disease who are given HRT. The study also suggested that aspirin and statins may be protective, a finding that certainly deserves intensive study. Statin therapy might be particularly helpful to women with lipid disorders. The risk may also be reduced by use of anticoagulation at times of increased thrombotic risk.

Antepartum Anticoagulation Is Not Always Needed for Women with a History of Venous Thromboembolism

Brill-Edwards P, Ginsberg JS, Gent M, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot In This Pregnancy Study Group. N Engl J Med. 2000;343:1439-44. [PMID: 11078768]

Women with a history of venous thromboembolism may be at increased risk for a recurrence when pregnant. The decision to give or withhold heparin before delivery remains controversial, in part because there are no accurate estimates of how frequently thromboembolism recurs when heparin is withheld. Some authorities have recommended prophylactic anticoagulation both during pregnancy and in the postpartum period. Most studies did not use objective testing to confirm thromboembolism, and some were retrospective studies of nonconsecutive patients. Brill-Edwards and colleagues' multicenter study, performed in Canada, is based on a prospectively assembled cohort of consecutive eligible women seen from 1994 through 1998 who had a history of venous thromboembolism and no known thrombophilia. The 125 participants were enrolled at or before 20 weeks' gestation. The patients did not receive anticoagulants during pregnancy but did take heparin and warfarin after birth. They continued to take warfarin for 4 to 6 weeks. If symptoms or signs of deep venous thrombosis occurred during pregnancy, the patient had serial compression ultrasonography of the proximal veins. Patients suspected of having pulmonary embolism underwent ventilation–perfusion lung scanning. Laboratory tests (for factor V Leiden, prothrombin gene mutation, anticardiolipin antibody, protein S, protein C, and antithrombin III) were done on blood samples obtained from 95 women.

Three women (2.4%) had antepartum episodes of venous thromboembolism: 2 had deep venous thrombosis and 1 had pulmonary embolism. They received low-molecular-weight heparin for the rest of their pregnancies. Three women received anticoagulation for a mean of 33 days after episodes of deep venous thrombosis occurred in the postpartum period. No patient had postpartum recurrence during warfarin prophylaxis. Nine episodes of suspected pulmonary embolism were investigated, but only one was confirmed (it was not fatal). Just over half the women tested had one or more laboratory abnormalities; the most common were a low plasma level of free protein S, heterozygosity for factor V Leiden, and heterozygosity for the prothrombin G20210A mutation. Only one woman with a low free protein S level had a true deficiency on subsequent testing. Excluding those with transiently low levels of free protein S, 4 of 25 women with abnormal test findings had recurrent venous thromboembolism, compared with only 2 of 70 women with normal test results (odds ratio, 6.5 [CI, 0.8 to 56.3]). Factor V Leiden carried the highest odds ratio. All three women with an antepartum recurrence of thromboembolism had a history of idiopathic venous thromboembolism, an abnormal laboratory result, or both. No recurrences developed among the 44 women who lacked laboratory evidence of thrombophilia and whose previous thrombotic episode correlated with a risk factor that was present only transiently.

The investigators believe that pregnant women do not need antepartum anticoagulation if a single past episode of thrombosis occurred during a time of increased risk, such as oral contraceptive use or pregnancy, providing that results of tests for thrombophilia are negative. It is important, however, to do these tests if withholding of anticoagulation is planned, with special attention paid to factor V Leiden. The authors recommend anticoagulation during the postpartum period for all women with a history of thrombosis. The most recent edition of the American College of Chest Physicians Guidelines on Antithrombotic Therapy summarizes current recommendations for anticoagulation in pregnancy (5).

Sickle-Cell Disease

Hydroxyurea Is Cost-Effective in Reducing the Frequency of Pain Crises in Adults with Sickle-Cell Disease

Moore RD, Charache S, Terrin ML, et al. Cost-effectiveness of hydroxyurea in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Am J Hematol 2000; 64:26-31. [PMID: 10815784]

Patients with sickle-cell disease are living increasingly longer lives, thanks in large part to effective penicillins and vaccination against pneumococcal pneumonia. More patients reach adulthood, at which point they incur adult medical problems: pulmonary hypertension, acute chest syndrome, renal insufficiency, cardiac conditions, and problems with transfusion. General internists will assume an increasingly active role, along with hematologists, in caring for these patients. Moore and colleagues analyzed the cost-effectiveness of hydroxyurea treatment for sickle-cell anemia using data from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. This randomized, placebo-controlled, double-blind trial enrolled approximately 300 adults with sickle-cell disease, all of whom reported having three or more painful crises each year. Hydroxyurea treatment reduced the frequency of these crises by half compared with placebo (6).

The authors estimated costs for all outpatient visits and inpatient stays due to pain crises, along with the costs of acute chest syndrome, analgesia, hydroxyurea treatment, monitoring, transfusions, and clinical visits. Annualized mean costs for hospitalization caused by painful crisis were $12 160 for patients given hydroxyurea and $17 290 for placebo recipients (difference, $5130 [CI, $60 to $10 200]; $P = 0.048$). Hospital admissions accounted for a majority of costs in both study groups. Patients treated with hydroxyurea had lower costs for transfusions, opiates, emergency department visits, and treatment for acute chest syndrome. The difference in the mean costs of care for chest syndrome was $830 (CI, $340 to $2000; $P = 0.16$). Mean total costs, including those for hydroxyurea and treatment monitoring, were $16 810 for hydroxyurea recipients and $22 020 for placebo recipients ($P > 0.2$). The difference was $5210 (CI, $610 to $11 030; $P > 0.2$).

These findings imply that the cost of prescribing hydroxyurea and monitoring its use in adults with painful crises of sickle-cell disease is more than compensated by reductions in the medical cost of treating painful crises. The investigators believe that hydroxyurea therapy is warranted for patients having three or more painful crises each year. Hydroxyurea therapy appears to be cost-effective in this setting compared with placebo, even though the total cost difference is not statistically significant. Even greater long-term savings may occur if this agent prevents chronic organ damage. Children are now receiving hydroxyurea, and a randomized trial is being planned to learn whether the drug will limit the adverse consequences of sickle-cell disease in very young children. Bone marrow transplantation may cure the disorder in pediatric patients if the right match is available, but this conclusion does not currently apply to adolescent or adult patients.

Pulmonary Infection and Fat Embolism Were Major Causes of Acute Chest Syndrome in a Prospective Study of Sickle-Cell Disease

Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med. 2000;342:1855-65. [PMID: 10861320]

Acute chest syndrome is now the most common cause of death in adults with sickle-cell disease. Infectious and noninfectious causes have been postulated and pulmonary fat embolism implicated, but the cause or causes remain uncertain and appropriate treatment therefore is controversial. Vichinsky and colleagues conducted a prospective study at 30 centers, analyzing 671 episodes of acute chest syndrome in 538 patients with a hemoglobin SS, hemoglobin SC, or hemoglobin SS–thalassemia phenotype. The criterion for a diagnosis was a new pulmonary infiltrate involving at least one complete lung segment, consistent with alveolar consolidation but not representing atelectasis. Management included antigen-matched blood transfusions depleted of leukocytes and lacking sickle cells, bronchodilator therapy, and bronchoscopy. There were guidelines for administering oxygen, respiratory therapy, fluids, antibiotics, and pain management. Blood and respiratory tract secretions were sampled for antibody testing, culture, DNA analysis, and histopathologic study.

Nearly half the patients had an admission diagnosis other than acute chest syndrome; in most of these patients, the admission diagnosis was vaso-occlusive crisis. In these cases, clinical and radiographic findings of acute chest syndrome became apparent an average of 2.5 days after admission. Patients typically were hypoxic at the time of diagnosis and had decreasing hemoglobin levels and progressive multilobar pneumonia. The mean hospital stay was 10.5 days. Mechanical ventilation was necessary in 13% of patients, 81% of whom recovered. Patients 20 years of age and older had a more severe course than younger patients. Neurologic events occurred in 11% of patients, nearly half of whom had respiratory failure. Matched transfusions improved oxygenation, and the rate of alloimmunization was 1%. One fifth of patients given bronchodilators improved clinically. The authors identified a specific cause in 38% of all episodes and in 70% of episodes for which complete data were available. Among the causes were pulmonary fat embolism and 27 different infectious agents, the most common being *Chlamydia pneumoniae*. Eighteen patients (3%) died, most commonly of pulmonary embolism or infectious bronchopneumonia. Infection contributed to 56% of the deaths. Mortality was 9% in patients older than 20 years.

Internists may be the first to encounter patients with sickle-cell anemia who develop acute chest syndrome. In adults, the initial symptoms may be dyspnea or pain in the extremities. Fat embolism and infections, including community-acquired pneumonia, are common causes. Most patients who require mechanical ventilation will recover if treated aggressively. The prognosis is improved by matched transfusions, broad-spectrum antibiotics (including a macrolide), and bronchodilator therapy.

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Chemotherapy for Older Patients with Newly Diagnosed, Advanced-Stage, Aggressive-Histology Non-Hodgkin Lymphoma: A Systematic Review

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Purpose: To conduct a systematic review assessing chemotherapeutic regimens in patients at least 60 years of age with previously untreated, advanced-stage, aggressive-histology non-Hodgkin lymphoma.

Data Sources: Computerized databases were searched for reports from 1966 to April 2000. Relevant journals, textbooks, and reference lists of published articles were hand searched. Abstract reports were not considered.

Study Selection: Randomized trials comparing different chemotherapy regimens were selected. Two independent assessors, who were blinded to authors, institution, and results of the report, reviewed the retrieved citations.

Data Extraction: One author abstracted data on patient characteristics, study quality score, survival, disease response and control, toxicity, and quality of life; pooling was not done because of study heterogeneity.

Data Synthesis: 12 randomized trials that compared chemotherapeutic regimens were reviewed. Progression-free and overall survival were improved when anthracycline-containing regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CTVP (cyclophosphamide, pirarubicin, vincristine, and prednisone), were compared with other regimens.

Conclusions: For treatment of older patients with advanced-stage, aggressive-histology lymphoma who do not have significant comorbid illnesses, an anthracycline-containing regimen, such as CHOP, given in standard doses and schedule, provides for superior outcomes compared with other regimens.

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Age strongly influences outcomes in patients with aggressive-histology non-Hodgkin lymphoma (1). Fewer clinical trials have tested treatment in older patients than in younger patients, and most conclusions about therapy for older patients with this disease have come from nonrandomized trials or studies in which the older patients constituted only a subset of a larger population. Several factors could account for differences in outcomes between younger and older patients with lymphoma: In brief, 1) differences in disease biology could result in more aggressive disease behavior, 2) altered pharmacokinetics and poorer host tissue tolerance may lead to a higher rate of adverse reactions, 3) comorbid illness may complicate treatment choices, and 4) the administration of less intensive chemotherapy may compromise disease control (2–6). Because half of the patients with aggressive-histology lymphoma are older than 65 years of age (7) and the proportion of older persons in the North American and European population is increasing (8), the optimal management of these patients is of considerable importance.

The International Prognostic Factors Project identified age older than 60 years as an important prognostic factor in aggressive-histology lymphoma. For younger patients with aggressive-histology lymphoma, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (9) is considered standard therapy on the basis of randomized trials that compared this regimen with second-generation and third-generation regimens (10). Because the International Prognostic Factors Project and many clinical trials have used 60 years of age or older to define older patients, our review uses this age criterion.

To assess the current evidence about the optimum treatment for older patients with aggressive-histology lymphoma, we conducted a systematic review designed to minimize bias and random error (11). Although several published reviews have addressed therapy for patients with lymphoma, including older patients, they have not used the methods of systematic review (3–5, 12, 13). In our systematic review, we summarize, critically appraise, and synthesize the results of randomized

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studies that assessed specific chemotherapy options in older patients with previously untreated, advanced-stage, aggressive-histology non-Hodgkin lymphoma.

METHODS

Search Strategies

We searched, without language restrictions (14, 15), the following databases: MEDLINE (reports published from 1966 to April 2000), EMBASE (1980 to March 2000), CANCERLIT (1983 to April 2000), Current Contents (1993 to April 2000), *Best Evidence* (1991 to April 2000), the Cochrane Library (issue 1, 2000), and an unpublished thesis database (UMI ProQuest [16]). Details about the search strategy are available from the authors on request. Tables of contents of hemato–oncology journals and reference lists from retrieved articles and textbooks were hand searched.

Study Selection

One author removed duplicate citations and citations dealing with other diseases from the MEDLINE, CANCERLIT, and EMBASE citation lists. Subsequently, two authors who were blinded to author names and institutional affiliations, journal name, publication year, and study results independently assessed the remaining citations on the basis of explicit inclusion and exclusion criteria. To be included, the study needed to be a randomized trial or an evidence-based practice guideline; the patients must have been 60 years of age or older and have had previously untreated, advanced-stage (any stage with B symptoms and stages II to IV [Ann Arbor staging system]), aggressive-histology (intermediate grade or high grade, Working Formulation [17]) non-Hodgkin lymphoma. Exclusion criteria were 1) the use of interferon, maintenance chemotherapy, or stem-cell transplantation or 2) HIV-related lymphoma. Citations were scored as "yes" if they met all inclusion criteria and "no" if they met an exclusion criterion. If citations met some of the inclusion criteria but met none of the exclusion criteria or if a clear judgment could not be rendered because of insufficient information, the citation was scored as "maybe." Citations from the other databases were assessed by using the same inclusion and exclusion criteria by one author in an unblinded fashion. The printed article was retrieved if at least one reviewer judged its citation as a "yes" or "maybe." In cases of disagreement (when only one reviewer judged a citation as "no"), the citation was adjudicated for eligibility by another author who was not involved in this stage of review. Abstracts were not considered because they usually provide information of a more preliminary nature. Subset analyses, although they may be misleading and require careful interpretation (18), were included if they contained data on the subset of patients 60 years of age or older.

We used PC-Agree software (20) to calculate κ agreement coefficients (19) by using quadratic weights in which partial credit was given for partial agreement (for example, yes–maybe vs. yes–no). To assess the reliability of our eligibility criteria, we used κ to quantify the agreement between reviewers beyond the degree of agreement that would be expected by chance alone. The interobserver κ was calculated for the two independent reviewers' scores (yes, maybe, no) of the blinded citations. The intraobserver κ was calculated for each of the two independent reviewers on the basis of 20 citations from MEDLINE that were randomly selected by using a random-numbers table. According to convention, we considered an acceptable κ to be 0.60 or higher (19).

Assessment of Study Quality

Methodologic quality was assessed by using a validated instrument for scoring the quality of randomized, controlled trials (21). The quality scores ranged from 0, which represents poor quality, to 5, which represents the best quality. A score was determined on the basis of whether 1) the randomization method was described, 2) the study was double-blinded, and 3) withdrawn participants were adequately described. The score was not used to determine study inclusion or quantitative weighting of results. We established that the study evidence needed to address clinically important outcomes, such as overall survival, any measure of the disease-control period (for example, time to treatment failure), or quality of life; reporting of response rates alone was insufficient. The conclusions about eligibility were based on the full reports of primary studies that described overall survival and any measure of disease control. Determination of whether to combine (pool) the results of the studies was based on the study sample, treatment regimens, and reported outcomes.

Table 1. **Reasons for Study Exclusion**

Reason for Exclusion	Studies, *n*
Other diseases were evaluated (for example, myeloma, Hodgkin disease, leukemia)	85
Transplantation or growth factor were used	79
Other interventions were evaluated	72
Citation was a review article	66
Age subgroup was not analyzed	59
Study was nonrandomized	56
Participants had low-grade, relapsed, or refractory non-Hodgkin lymphoma	46
Citation was a basic science article	22
Patients with HIV were included	9
Citation was an abstract	7
Patients were too young	7
Study was reported subsequently in full form	3
Total*	511

* Duplicate studies were excluded; studies may have been excluded for multiple reasons.

RESULTS

Retrieved Articles

The search strategy resulted in a total of 289 citations in MEDLINE, 106 in CANCERLIT, and 391 in EMBASE. After one author initially screened the citations, two blinded reviewers independently assessed a total of 385 citations for eligibility. The interobserver κ assessing the agreement beyond chance alone for the blinded databases was 0.83, and the intraobserver κ values for each of the blinded assessors were 0.60 and 0.80. **Table 1** summarizes the reasons for study exclusion. Of 76 total entries found by searching the Current Contents database, none represented additional eligible studies. Likewise, searching the other databases revealed no reports.

Data Synthesis

Twelve full-length reports of randomized trials were examined and are summarized in **Tables 2** and **3**. Three studies (22–24) received a quality score of 3, 8 studies (25–32) received a score of 2, and 1 study (33) received a score of 1. Studies were grouped into one of three categories according to whether the study compared 1) regimens that differed only in the specific anthracycline agent used (22, 25–27), 2) a fractionated chemotherapy schedule with the standard schedule for the same chemotherapy (28), or 3) regimens that differed by some other criteria (23, 24, 29–33). The age criterion differed among these 12 randomized studies, with the minimum age for older patients ranging between 60 and 70 years. Because of differences in the hypotheses tested, the heterogeneity of the inclusion criteria for age, and the variety of chemotherapy regimens used, we considered statistical pooling of these data to be inappropriate.

Comparisons Testing Regimens with Anthracycline Substitution

We examined four full reports in which regimens were compared to test the substitution of the anthracycline component (**Tables 2** and **3**). Sonneveld and colleagues (22) randomly allocated 148 patients at least 60 years of age to receive CHOP or a similar regimen that substituted mitoxantrone for doxorubicin (CNOP). In this study, which received a quality score of 3, the researchers analyzed the results on an intention-to-treat basis; sample-size calculations were reported, and the groups were balanced at baseline. The minimum cardiac ejection fraction required was at least 0.40, which is lower than that allowed in other studies. In contrast to the standard treatment cycle for CHOP—full-dose administration every 3 weeks—the treatments in this trial were administered at weekly intervals for 4 weeks (9). In comparison with patients receiving CNOP, patients receiving CHOP had a superior median and 3-year overall survival, but no difference was detected in the rate of 3-year disease-free survival. The overall toxicity did not differ among patients 60 to 70 years of age, patients 70 to 75 years of age, and those older than 75 years of age. These results favoring doxorubicin are consistent with those seen in younger patients (34).

Aviles and coworkers (25) randomly assigned 169 patients to one of two regimens containing dose-escalated anthracycline: One group received cyclophosphamide, epirubicin, vincristine, prednisone, and bleomycin (CEOP-Bleo), and the other group received the same regimen except that idarubicin was substituted for epirubicin (CIOP-Bleo). This study, which received a quality score of 2, used groups that were balanced at baseline; however, the study did not explicitly report the number of patients who could not tolerate the dose escalation or whether such patients were included in the intention-to-treat analysis. Patients receiving CEOP-Bleo had a superior 3-year overall survival rate (72% among CEOP-Bleo recipients vs. 34% among CIOP-Bleo recipients; $P < 0.01$). Although this study suggests a ben-

Table 2. **Randomized Trials of Chemotherapy: Patients and Therapy***

Study	Type of Analysis	Patient Characteristics				Chemotherapy Regimens	Principle Tested
		Age, *y*	Patients, *n*	Disease Stage†	Pathology		
Sonneveld et al. (22)	Primary	≥60	148	II (bulky disease), III, IV	Diffuse mixed, diffuse large cell, immunoblastic	CHOP vs. CNOP	Substitution of mitoxantrone for doxorubicin
Aviles et al. (25)	Primary	≥60	169	NS	Diffuse large cell, small noncleaved cell, immunoblastic, anaplastic large cell	CEOP-B vs. CIOP-B	Substitution of epirubicin for idarubicin
Aoki et al. (26)	Primary	≥65	37	I–IV	Follicular medium cell, diffuse small cell, diffuse mixed, diffuse large cell, diffuse pleomorphic	Low-dose CHOP vs. T-COP vs. T-COPE	Substitution of doxorubicin for pirarubicin and the addition of etoposide
Delena et al. (27)	Subgroup	≥60	24	Any bulky disease with B symptoms	Intermediate grade or high grade (Working Formulation)	CHOP-B vs. CEOP-B	Substitution of epirubicin for doxorubicin
Meyer et al. (28)	Primary	≥65	38	IB, IIA (bulky disease), IIB–IV	Follicular large cell, diffuse small cleaved cell, diffuse mixed, diffuse large cell, immunoblastic	CHOP vs. chop‡	Weekly schedule fractionation
Tirelli et al. (23)	Primary	≥70	120	II–IV	Intermediate grade, high grade (Working Formulation) excluding small noncleaved cell, lymphoblastic lymphoma	CHOP vs. VMP	Standard vs. presumed less-toxic chemotherapy
Bastion et al. (29)	Primary	≥70	453	I (bulky), II–IV	Follicular large cell, diffuse small cleaved cell, diffuse mixed, diffuse large cell, immunoblastic, small noncleaved cell	CTVP vs. CVP	Evaluating the usefulness of the anthracycline factor
Jelic et al. (32)	Primary	≥65	47	I (bulky), II–IV	Diffuse large cell	BEP vs. MEP	Substitution of mitoxantrone for BCNU
Montserrat et al. (33)	Subgroup	≥60	78	II–IV	Follicular large cell, diffuse small cleaved cell, diffuse mixed, diffuse large cell, immunoblastic	CHOP vs. ProMACE-CytaBOM	CHOP vs. third-generation regimen
Cooper et al. (24)	Subgroup	≥60	77	I (bulky), II–IV	Follicular large cell, diffuse small cleaved cell, diffuse mixed, diffuse large cell, immunoblastic	CHOP vs. MACOP-B	CHOP vs. third-generation regimen
Gordon et al. (30)	Subgroup	≥60	167	III–IV	Diffuse mixed, diffuse large cell, immunoblastic	CHOP vs. m-BACOD	CHOP vs. second-generation regimen
Silingardi et al. (31)	Subgroup	>60	71	IB–IV	Intermediate grade, high grade	ProMECE-CytaBOM vs. MACOP-B	Comparison of third-generation regimens

* BCNU = bischloroethylnitrosourea (carmustine); BEP = BCNU, etoposide, prednisone; CEOP-B = cyclophosphamide, epirubicin, vincristine, prednisone, bleomycin; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CHOP-B = cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin; CIOP-B = cyclophosphamide, idarubicin, vincristine, prednisone, bleomycin; CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone; CTVP = cyclophosphamide, pirarubicin, vincristine, prednisone; CVP = cyclophosphamide, vincristine, prednisone; CytaBOM = cytarabine, bleomycin, vincristine, methotrexate, prednisone, leucovorin; MACOP-B = methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; m-BACOD = methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone, leucovorin; MEP = mitoxantrone, etoposide, prednisone; NS = not specified; ProMACE = cyclophosphamide, doxorubicin, etoposide; ProMECE = cyclophosphamide, epirubicin, etoposide; T-COP = pirarubicin, cyclophosphamide, vincristine, prednisone; T-COPE = pirarubicin, cyclophosphamide, vincristine, prednisone, etoposide; VMP = teniposide, mitoxantrone, prednimustine.

† According to the Ann Arbor staging system.

‡ CHOP, conventional schedule, was compared with modified-dose CHOP (chop), administered in one-third doses weekly for 3 weeks.

efit of epirubicin compared with idarubicin, how these regimens compare with standard-dose CHOP is unknown.

Aoki and colleagues (26) randomly assigned 37 patients to receive 1) low-dose CHOP, 2) the same regimen except with substitution of pirarubicin for doxorubicin (THP-COP), or 3) THP-COP with etoposide added (THP-COPE). This study, which received a quality score of 2, did not include an intention-to-treat analysis and did not describe the sample-size calculations. The 2-year survival rate did not differ among treatment groups; however, the study was underpowered to determine whether important differences could be detected.

In Delena and coworkers' subgroup analysis (27) of older patients randomly assigned to a regimen that contained epirubicin or doxorubicin, the complete response rate did not differ between groups.

Table 3. **Randomized Trials of Chemotherapy: Results***

Study	Regimens Compared	Disease Response	*P* Value	Disease Control	*P* Value	Overall Survival	*P* Value
Sonneveld et al. (22)	CHOP vs. CNOP	Complete response: 49% vs. 31%	0.03	Median disease-free survival: 27 mo vs. 15 mo; Survival (at 3 y): 17% vs. 13%	>0.2 0.12	Median 26 mo vs. 12 mo; Survival at 3 y: 42% vs. 26%	0.029 0.034
Aviles et al. (25)	CEOP-B vs. CIOP-B	Complete response: 71% vs. 48%	0.003	Relapse-free survival (at 3 y)†: 73% vs. 37%	<0.01	At 3 y: 72% vs. 34%	<0.01
Aoki et al. (26)	Low-dose CHOP vs. T-COP vs. T-COPE	Overall response: 63.6% vs. 80% vs. 87.5%	>0.2	NS	–	At 2 y: 18% vs. 58% vs. 48%	–
Delena et al. (27)	CHOP-B vs. CEOP-B	Complete response: 50% vs. 71%	>0.2	NS	–	NS	–
Meyer et al. (28)	CHOP vs. chop‡	Complete response: 68% vs. 74%	0.09	Progression-free survival (at 2 y): 57% vs. 46%	0.16	At 2 y: 74% vs. 51%	0.05
Tirelli et al. (23)	CHOP vs. VMP	Complete response: 45% vs. 27% Overall response: 77% vs. 50%	0.06 0.01	Median progression-free survival†: 26 mo vs. 8 mo	0.002	Median‡: 36 mo vs. 13 mo	0.004
Bastion et al. (29)	CTVP vs. CVP	Complete response: 47% vs. 32%; Progressive disease: 21% vs. 39%	<0.001	Time to treatment failure (at 5 y): 24% vs. 14%	<0.05	At 5 y: 27% vs. 19%	<0.05
Jelic et al. (32)	BEP vs. MEP	Overall response: 59% vs. 60%	>0.2	NS	–	At 2 y: 30% vs. 50%	>0.2
Montserrat et al. (33)	CHOP vs. ProMACE-CytaBOM	Complete response: 56.5% vs. 54%	>0.2	NS	–	NS	–
Cooper et al. (24)	CHOP vs. MACOP-B	Complete response: 67% vs. 43%	0.04	Failure-free survival: 46% vs. 45%	–	At 4 y: 48% vs. 49%	–
Gordon et al. (30)	CHOP vs. m-BACOD	Complete response: 49% vs. 62%	0.09	NS	–	NS	–
Silingardi et al. (31)	ProMECE-CytaBOM vs. MACOP-B	Complete response: 52% vs. 68%	0.2	NS	–	NS	–

* Results are shown in the same order as their corresponding chemotherapy regimens. BCNU = bischloroethylnitrosourea (carmustine); BEP = BCNU, etoposide, prednisone; CEOP-B = cyclophosphamide, epirubicin, vincristine, prednisone, bleomycin; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CHOP-B = cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin; CIOP-B = cyclophosphamide, idarubicin, vincristine, prednisone, bleomycin; CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone; CTVP = cyclophosphamide, pirarubicin, vincristine, prednisone; CVP = cyclophosphamide, vincristine, prednisone; CytaBOM = cytarabine, bleomycin, vincristine, methotrexate, prednisone, leucovorin; MACOP-B = methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; m-BACOD = methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone, leucovorin; MEP = mitoxantrone, etoposide, prednisone; NS = not specified; ProMACE = cyclophosphamide, doxorubicin, etoposide; ProMECE = cyclophosphamide, epirubicin, etoposide; T-COP = pirarubicin, cyclophosphamide, vincristine, prednisone; T-COPE = pirarubicin, cyclophosphamide, vincristine, prednisone, etoposide; VMP = teniposide, mitoxantrone, prednimustine.

† Estimates taken from Kaplan–Meier plots.

‡ CHOP, conventional schedule, was compared with modified-dose CHOP (chop), administered in one-third doses weekly for 3 weeks.

Comparisons Testing Regimens with Chemotherapy Schedule Fractionation

Meyer and colleagues (28) tested received dose intensity in a randomized, phase II trial. They assigned 38 patients at least 65 years of age who had no significant comorbid illness to receive a conventional CHOP regimen (full doses given every 3 weeks) or a dose-modified regimen of one-third doses administered weekly (chop). This study received a quality score of 2; baseline patient characteristics were balanced, patient data were analyzed on an intention-to-treat basis, and sample-size calculations were reported. The sample size of this trial was based on a comparison of the received dose intensities of the two regimens, and no dose-intensity differences were detected. Although no difference in 2-year progression-free survival was detected, 2-year overall survival was of borderline significance in favor of CHOP. No statistically significant differences were seen in important toxicities; however, 47% of patients receiving standard CHOP compared with 26% of patients receiving weekly chop experienced at least one episode of neutropenic fever.

Comparisons of Regimens Differing by Other Criteria

The seven studies comparing regimens that differed according to other criteria are summarized in **Tables 2** and 3. Four of these studies compared CHOP with another regimen (23, 24, 30, 33), and three studies compared regimens that did not include CHOP (29, 31, 32).

A trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Cooperative Study Group (23) randomly allocated 120 patients at least 70 years of age to receive CHOP or a regimen of etoposide, mitoxantrone, and prednimustine (VMP). The quality score for this study was 3. The researchers did not perform an intention-to-treat analysis or provide sample-size calculations, and the groups were slightly imbalanced at baseline. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3 received 75% of the full dose for the initial cycle. Patients receiving CHOP had a longer median progression-free survival and overall survival. Moreover, patients receiving CHOP had lower rates of progression and relapse of lymphoma but had significantly more gastrointestinal and neurologic toxicity and a small trend toward more cardiovascular toxicity.

The Groupe d'Etude des Lymphomes de LAdulte (GELA) (29) randomly assigned 453 patients who were at least 70 years of age to a regimen of cyclophosphamide, teniposide, and prednisone (CVP) or the same regimen with pirarubicin added (CTVP). This study scored 2 on the quality scale. The researchers did not perform an intention-to-treat analysis or present sample-size calculations; the patient groups had minor imbalances at baseline. Compared with patients receiving CVP, patients receiving CTVP had a lower rate of progressive disease, an improved median time to treatment failure and 5-year failure-free survival rate, and a higher rate of 5-year overall survival. In terms of toxicity, patients receiving CTVP had more mucositis and more frequent and prolonged hospitalizations. This trial also showed that progressive disease was the most common cause of death.

Jelić and colleagues (32) randomly assigned 47 patients older than 64 years of age to receive bischloroethylnitrosourea (BCNU), etoposide, and procarbazine or to receive mitoxantrone, etoposide, and procarbazine (MEP). In marked contrast to other studies, 47% of patients had preexisting comorbid disease, including heart failure, angina, hypertensive heart disease, stroke, and chronic renal failure. This report, which received a quality score of 2, had no sample-size calculations or intention-to-treat analysis. The study groups were somewhat imbalanced at baseline, possibly because enrollment into the group receiving MEP was closed prematurely as a result of toxic effects. No difference was detected in the 2-year overall survival rate, although the study was underpowered to detect such differences. Two-year overall survival was lower in patients with comorbid illness than in patients without comorbid illness (17% vs. 60%; $P < 0.001$).

Three subgroup analyses (24, 30, 33) compared use of CHOP with use of second-generation and third-generation regimens in older patients. Differences were not detected in failure-free or overall survival. Another subgroup analysis (31) showed no difference in complete response rate in older patients who were randomly assigned to one of two third-generation regimens (31).

DISCUSSION

We systematically and comprehensively searched the literature for studies of chemotherapy in older patients with previously untreated, aggressive-histology non-Hodgkin lymphoma. We used systematic review methods, including searching an extensive computerized database with no language restrictions, hand searching, evaluating the identified reports in a blinded manner according to study selection criteria, and assessing the quality of the eligible studies.

Our analysis shows that in older patients with previously untreated, aggressive-histology lymphoma who have no significant underlying comorbid illness, survival and disease control were improved when an anthracycline-containing regimen such as CHOP or CTVP was compared with a regimen that omitted the anthracycline (CVP) (29), used a substituted anthracycline (CNOP) (22), or was designed to be less toxic (VMP) (23). The role of pirarubicin or epirubicin in a CHOP regimen compared with that of doxorubicin is unknown, and well-designed studies comparing standard doses of the different anthracyclines are needed. Weekly fractionation of the standard chemotherapy schedule of CHOP (28), chop, did not improve dose intensity and did not appear to improve any other outcomes. The evidence indicates that CHOP (or CTVP) should be the standard against which new treatments are compared, as is the case with the testing of therapeutic regimens in younger patients. Although we defined older patients for our review as those older than 60 years of age, age is a continuous prognostic variable because patients older than 70 years of age have inferior outcomes compared with patients 60 to 70 years of age (35). Although our review demonstrates that CHOP should be the standard therapy for patients older than 60 years of age, it also shows that this standard applies to patients older than 65, or even 70, years of age. We therefore conclude that age should not be used to determine therapy for patients who have no important comorbid conditions and no specific preferences about the balance of treatment benefits versus toxicity.

Because all of the trials except one (32) excluded older patients with comorbid illness, the results of our overview may not apply to all elderly patients with lymphoma. In the randomized study by Jelić and colleagues (32), comorbid illness had no effect on initial performance status but was associated with significantly worse overall survival. Chen and colleagues (36) described outcomes in older patients who met at least one exclusion criterion for a randomized, phase II trial (28) and who were treated with a variety of chemotherapy regimens. The 5-year overall survival was 10% in the excluded patients and 44.3% in the randomly assigned patients ($P < 0.001$). In one survey (37), 61% of patients 70 years or older with non-Hodgkin lymphoma had at least one comorbid condition compared with 20% of patients younger than 60 years of age. This shows that older patients have a high prevalence of comorbid illness, and those with significant comorbid illness do poorly. In addition, this highlights problems of patient selection and the generalizability of results from randomized, controlled trials.

Our review demonstrates that in comparison with regimens designed for specific testing in older patients, treatment with CHOP was associated with improvements in disease control and survival but also with greater toxicity. Because older patients may be more susceptible to the toxic effects of chemotherapy, measures to reduce toxicity may be particularly important. Use of growth factors, such as granulocyte colony-stimulating factor (G-CSF), has been hypothesized as a means of reducing the myelotoxic and infectious risks from standard-dose chemotherapy. The use of G-CSF in older patients has been reported in three randomized trials (38–40), only one of which has been fully reported (38). These trials have shown that primary therapy with G-CSF after a first cycle of chemotherapy reduces the degree of neutropenia and the incidence of infections but does not improve disease control or overall survival. Evidence-based guidelines exist for the use of G-CSF in patients receiving myelosuppressive chemotherapy (41, 42), although these guidelines do not specifically address older patients with lymphoma.

Recently, interim results in abstract form (43) were reported by the investigators of a randomized trial that tested the addition of an anti–CD-20 monoclonal antibody, rituximab, to standard CHOP in patients 60 to 80 years of age with previously untreated, advanced-stage, diffuse large–B-cell lymphoma. Preliminary results have shown that the addition of ritumixab to CHOP was associated with improvements in 1-year event-free survival (69% vs. 49%; $P < 0.001$) and 1-year overall survival (86% vs. 68%; $P < 0.01$). These results appear promising but require further follow-up.

In summary, the results from randomized trials suggest that in the absence of significant comorbid illness or strong patient preferences, age should not be used as a variable to modify therapy and that older patients with newly diagnosed, advanced-stage, aggressive-histology non-Hodgkin lymphoma should be offered the same standard therapy as younger patients—CHOP. Special issues complicate the generalizability of trial results to all older patients, and caution should therefore be used in applying these conclusions to patients with comorbid conditions. The mature results of trials that have to date reported only preliminary findings will help elucidate the roles of growth factors as supportive measures and monoclonal antibody therapy as an antitumor agent. Further research is needed to explore treatment strategies in older patients with comorbid illnesses.

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a coral reef hidden, then revealed.
Having breakfast on our rented verandah
I watch the pale blue Gulf of Mexico
disappear into the pale blue sky
as a mother walks her three year old
toward the sand. When he complains
about the rough path, she lifts him
and his red bucket to her hip.
In Pittsburgh, when my father was dying,
I dripped morphine under his tongue
every hour, every half hour, every twenty minutes.
***Don't be afraid,* the hospice nurse told me,**
to give whatever will carry him.

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Measuring Quality: Are We Ready To Compare the Quality of Care among Physician Groups?

Americans want high-quality health care, but they are not confident that they are getting it. Nor are Americans confident that they have valid information about the quality of their care. The public, health care purchasers, health system managers, and health policymakers are increasingly interested in getting more, and more accurate, information on the quality of care offered by different health care providers. The gap between the data they want and the data they can get may be widening as the public's expectations exceed what the health system can provide.

Information on quality of care has three principal uses: to support accountability, to inform quality improvement efforts, and to guide choice. This editorial focuses on the role of quality measures in guiding choice, although the three uses are entwined at many levels. Forty-two percent of respondents to a consumer survey conducted by the Agency for Healthcare Research and Quality (AHRQ) and the Kaiser Family Foundation stated that high-quality care was their most important concern in choosing a health plan (1). This evidence that consumers and purchasers want information on quality is encouraging to people who still hope that the public will base its purchasing decisions on quality of care rather than simply cost. According to the elusive "business case for quality," providers who offer superior care will have more patients and higher payments.

Information about quality can improve care at several points of leverage in the health care system. Such information should be able to guide consumers' choices of health plan, hospital, nursing home, or doctor. Having the opportunity to consider data on quality should give patients and their families more confidence that they are making the right choices. Feeding information on quality of care back to clinicians and health care institutions should help them identify areas for improvement. Purchasers of health care should be able to use metrics of quality to implement the principles of value-based purchasing. The prerequisite for action is an interested, demanding public that has access to information and can make real choices, which is possible only if people have more than one plan from which to choose.

The proponents of value-based purchasing argue that the opportunity to choose high-performing providers will improve health care by creating competition on the basis of quality. However, the premise of value-based purchasing is accurate measures of value. Absent these, patients may not get the best-quality physicians, and the best-quality physicians may not get the patients. The dearth of accurate quality measures is a major obstacle to value-based purchasing.

A second obstacle is access to information about quality, even when such data exist. Few Americans have seen information about the quality of health care providers. In a survey published in 1997, only 27% of Americans reported ever seeing information comparing providers' quality; fewer than 15% had ever used this information (2). However, respondents thought that such information would be useful for decision making (3). Why is it that a public that wants information on the quality of its health care cannot get it, and then, when the information is available, does not often use it? We do not yet know the answer to this question.

In this issue, Greenfield and colleagues present the results of a study that illustrates several ways in which one type of quality measure, comparisons of physician groups, can lead the value-based decision maker astray (4). By examining diabetes care in 29 physician practices, the authors showed that an accurate conclusion about whether endocrinologists or general internists provide better care requires adjustment for differences in case-mix. This finding would not surprise most physicians. However, at a far more subtle level, Greenfield and colleagues also found that performance measures could be misleading unless one considered the possibility that physicians gravitate toward practicing with like-minded physicians (clustering). When clustering occurs, individual patients are not entirely independent of one another, which means that more patients are required to make statistically valid comparisons between groups. Without adjustment for clustering, endocrinologists appeared to give better diabetes care. With adjustment, endocrinologists and generalists provided care of comparable quality.

This study by Greenfield and colleagues prompts us to ask whether the data that compare physician groups—and, by extension, the data that compare individual physicians, hospitals, or health plans—are fair to those being measured and useful to decision makers. Consumers should ask this question, but they should ask it in the form of three related questions. Do the data take into account the case-mixes of the groups' patient panels? Is the number of cases in each group large enough to accurately represent typical practice patterns? Do the performance measures reflect the possibility that patients and physicians cluster into certain types of practices?

Value-based decision makers must have access to better measures of quality. Such access has not been available. However, there are now emerging several examples of purchasers who can use reports on physician performance. For example, PacifiCare's Quality Index for California includes rankings of 120 physician groups that are based on a large number of clinical and satisfaction criteria (5). Another California plan, HealthNet, has issued member satisfaction reports that are disease specific and are reported by physician group (6).

So, are we ready to compare the quality of care among physician groups? The technical barriers to performance reports remain formidable. As the unit of measurement becomes smaller (an individual physician as opposed to a physician group or a hospital), the sample size challenge worsens. Leveling the playing field between practices by taking account of the types and severity of clinical problems (the case-mix challenge) is difficult. Finding quality indicators that are easy to collect during day-to-day practice represents yet another barrier. The study by Greenfield and colleagues is important because the authors overcame some of these serious methodologic barriers to making fair comparisons of physician groups. In addition, this study points the way to lasting success in providing the public with the information it wants and deserves.

As providers and the public become more comfortable with these measures and their fairness, we will probably see them being used not just by purchasers who want to make value-based decisions but also by providers who want to improve the care in their practice; demonstrate that they give excellent care; and provide the public with the accountability and informed, value-based choice that it wants. The emerging demand for comparisons of practices according to the quality of care they provide is gradually leading to better measures and methodologic advances in using the data. These advances are beginning to show up in the form of high-quality data that more closely fit the desires of purchasers, patients, and providers. We are getting close to a historic moment when we can set in motion the upward spiral that can occur when there is a business case for quality.

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Disease Prevention Guidelines from the U.S. Preventive Services Task Force

This issue marks the first of a series of articles describing the state of the art and science of disease prevention, as interpreted by the U.S. Preventive Services Task Force (USPSTF). I write to introduce *Annals* readers to the USPSTF and to describe this journal's role in the guidelines field.

In 1983, Dr. Edward Huth, editor of *Annals* from 1970 to 1993, published a medical practice guideline on the management of diabetes mellitus (1). It was the product of a new American College of Physicians program, the Clinical Efficacy Assessment Program, which began in 1980 under the direction of Dr. Robert Moser (then the Executive Vice President of the College). The College was one of the first professional organizations to establish a guidelines program. CEAP, as it was known then, set a standard that the best guidelines programs still strive to emulate. The basic approach was to review the literature on a topic, describe the pertinent findings from the very best articles, develop recommendations based on that evidence, and publish the recommendation in *Annals*. The guideline appeared in a short article, called the position paper. A longer accompanying article, the background paper, described the evidence. *Annals* subjected the background paper to peer review, but the position paper stood as the College's statement on the clinical question at hand. The College has published a book, *Common Screening Tests* (2), and guidelines that helped to frame the dialog on cholesterol screening (3, 4) and prostate cancer screening (5–7), among other controversial screening topics.

The model for both the USPSTF and the College's guidelines program is the Canadian Task Force on the Periodic Health Examination, which released its first report in 1979. Dr. J. Michael McGinnis, who was then Director of the Office of Disease Prevention and Health Promotion in the U.S. Department of Health and Human Services, convened the first USPSTF in 1984. From the beginning, the Task Force has been federally funded but independent. Most of the USPSTF members have been primary care physicians with expertise in the evaluation of evidence. The first USPSTF issued its report in 1989 in the form of a book titled *Guide to Clinical Preventive Services* (8). This book sold very well and established the Task Force as an authoritative source of guidance about evidence-based preventive medicine. In 1990, the second USPSTF convened to update the guidelines of the first Task Force. In 1995, it issued a much-expanded set of guidelines in the second edition of its report (9). The third USPSTF convened in 1998 under the sponsorship of the Agency for Healthcare Research and Quality. This agency contracts with Evidence-Based Practice Centers in North Carolina and Oregon to review the literature, cull the best studies, collate the evidence, and draft the evidence reports. The staff of these centers consists of experts in the tasks of evaluating research. The members of the third Task Force include representatives of internal medicine, family practice, pediatrics, obstetrics–gynecology, and nursing, as well as experts on behavioral medicine and cost-effectiveness analysis.

The College, the Canadian Task Force, and the USPSTF have been leaders in the field of evidence-based guidelines for disease prevention. Although the three organizations are independent of one another, their recommendations have usually agreed closely; this concordance testifies to the robustness of a rigorous evidence-based approach to practice guideline development. With two strong organizations specializing in guidelines for disease prevention, the College guidelines program has decided to focus on other topics. Therefore, by publishing USPSTF guidelines that pertain to adults, *Annals* will give its readers a view of disease prevention that they would not get from the College's guideline program.

The USPSTF plans to publish its reports in medical journals. We do not have a formal understanding with the Task Force; they are free to publish elsewhere, and we are free to decide which topics have the highest claim on our readers' attention. In a manner that is analogous to the College's guideline program, most Task Force reports will consist of two articles. The Task Force members write a brief clinically oriented summary (Recommendations and Rationale). Members of the Evidence-Based Practice Centers write the background article, which contains a systematic review of the evidence. In the interest of conserving expensive page space, we may publish some of the longer tables only on www

.annals.org, the *Annals* Web site. The Task Force is trying many strategies to disseminate the preventive services guidelines. We will do our part by placing their reports on the public-access part of our Web site so that anyone can access the electronic version of both articles. The Task Force will also publish the articles on their Web site (www.ahrq.gov/clinic/uspstfix.htm) and on the National Guideline Clearinghouse Web site (www.guidelines.gov).

Dr. Christine Laine, our senior deputy editor, will be the editor for this series. We will send all articles for external peer review. Dr. Cynthia Mulrow and I have both been Task Force members, and we are coauthors on some Task Force background articles. Accordingly, we will recuse ourselves from discussions of work in which we participated as authors.

Annals will publish USPSTF reports because we believe that internists should have convenient access to the best evidence about disease prevention, a core activity for most internists. Publishing USPSTF reports will help to make *Annals* a "must read" for health professionals and for the public, which is exactly the role that we seek to play.

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Editor

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CLINICAL GUIDELINES

Aspirin for the Primary Prevention of Cardiovascular Events: Recommendation and Rationale

U.S. Preventive Services Task Force*

This statement summarizes the recommendation of the third U.S. Preventive Services Task Force (USPSTF) for aspirin for the primary prevention of cardiovascular events, as well as the supporting scientific evidence. The complete information on which this statement is based, including evidence tables and references, can be found in a companion article in this issue. Copies of this document, the summary of the evidence, and the systematic evidence review can be obtained through the USPSTF Web site (www.ahrq.gov/clinic/uspstfix.htm) and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (800-358-9295).

Ann Intern Med. 2002;136:157-160. www.annals.org

See related article on pp 161-172 and editorial comment on pp 155-156.

SUMMARY OF THE RECOMMENDATION

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians discuss aspirin chemoprevention with adults who are at increased risk for coronary heart disease (see Clinical Considerations). Discussions with patients should address both the potential benefits and harms of aspirin therapy. This is a **grade A recommendation.** (See **Appendix Table 1** for a description of the USPSTF classification of recommendations.)

The USPSTF found good evidence that aspirin decreases the incidence of coronary heart disease in adults who are at increased risk for heart disease. It also found good evidence that aspirin increases the incidence of gastrointestinal bleeding and fair evidence that aspirin increases the incidence of hemorrhagic strokes. (See **Appendix Table 2** for a description of the USPSTF classification of levels of evidence.) *The USPSTF concluded that the balance of benefits and harms is most favorable in patients at high risk for coronary heart disease (those with a 5-year risk ≥ 3%) but is also influenced by patient preferences.*

CLINICAL CONSIDERATIONS

Decisions about aspirin therapy should take into account overall risk for coronary heart disease. Risk assessment should include asking about the presence and severity of the following risk factors: age, sex, diabetes, elevated total cholesterol levels, low levels of high-density lipoprotein cholesterol, elevated blood pressure, family history (in younger adults), and smoking. Tools that incorporate specific information on multiple risk factors provide more accurate estimation of cardiovascular risk than categorizations based simply on counting the numbers of risk factors (www.med-decisions.com) (1).

Men older than 40 years of age, postmenopausal women, and younger persons with risk factors for coronary heart disease (for example, hypertension, diabetes, or smoking) are at increased risk for heart disease and may wish to consider aspirin therapy. The **Table** shows how estimates of the type and magnitude of benefits and harms associated with aspirin therapy vary with an individual's underlying risk for coronary heart disease. Although balance of benefits and harms is most favorable in high-risk persons (those with a 5-year risk ≥ 3%), some persons at lower risk may consider the potential benefits of aspirin to outweigh the potential harms.

Discussions about aspirin therapy should focus on potential coronary heart disease benefits, such as prevention of myocardial infarction, and potential harms, such as gastrointestinal and intracranial bleeding. Discussions should take into account individual preferences and risk aversions concerning myocardial infarction, stroke, and gastrointestinal bleeding. Although the optimal timing and frequency of discussions related to aspirin therapy are unknown, reasonable options include every 5 years in middle-aged and older persons or when other cardiovascular risk factors are detected.

Most participants in the primary prevention trials of aspirin therapy have been men between 40 and 75 years of age. Current estimates of benefits and harms may not

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* For a list of the members of the U.S. Preventive Services Task Force, see the Appendix.

Table. **Estimates of Benefits and Harms of Aspirin Given for 5 Years to 1000 Persons with Various Levels of Baseline Risk for Coronary Heart Disease***

Benefits and Harms	Baseline Risk for Coronary Heart Disease over 5 Years†		
	1%	3%	5%
Total mortality	No effect	No effect	No effect
Coronary heart disease events, *n*	1–4 avoided	4–12 avoided	6–20 avoided
Hemorrhagic strokes, *n*‡	0–2 caused	0–2 caused	0–2 caused
Major gastrointestinal bleeding events, *n*§	2–4 caused	2–4 caused	2–4 caused

* Estimates are based on a relative risk reduction of 28% for coronary heart disease events in aspirin-treated patients and assume that risk reductions do not vary significantly by age. Adapted from reference 2.

† Nonfatal acute myocardial infarction and fatal coronary heart disease. Five-year risks of 1%, 3%, and 5% are equivalent to 10-year risks of 2%, 6%, and 10%, respectively.

‡ Data from secondary prevention trials suggest that increases in hemorrhagic stroke may be offset by reduction in other types of stroke in patients at very high risk for cardiovascular disease (≥10% 5-year risk).

§ Rates may be two to three times higher in persons older than 70 years of age.

be as reliable for women and older men. Although older patients may derive greater benefits because they are at higher risk for coronary heart disease and stroke, their risk for bleeding may be higher. Uncontrolled hypertension may attenuate the benefits of aspirin in reducing coronary heart disease.

The optimum dose of aspirin for chemoprevention is not known. Primary and secondary prevention trials have demonstrated benefits with a variety of regimens, including 75 mg/d, 100 mg/d, and 325 mg every other day. Dosages of approximately 75 mg/d seem to be as effective as higher doses; whether dosages below 75 mg/d are effective has not been established. Enteric-coated or buffered preparations do not clearly reduce adverse gastrointestinal effects of aspirin. Uncontrolled hypertension and concomitant use of other nonsteroidal anti-inflammatory agents or anticoagulants increase risk for serious bleeding.

SCIENTIFIC EVIDENCE

Epidemiology and Clinical Background

Cardiovascular disease, including ischemic coronary heart disease, stroke, and peripheral vascular disease, is the leading cause of death in the United States (3). Yearly, over 1 million Americans experience new or recurrent myocardial infarction or fatal coronary heart disease. Most events occur in older persons and those with recognized risk factors for cardiovascular disease, including high cholesterol level, high blood pressure, diabetes, or a history of smoking. The early-documented and clear success of aspirin in preventing further clinical disease in some patients with known heart disease (secondary prevention) raised interest in aspirin as a potential primary preventive intervention in men and women without known heart disease (4). Two early randomized trials of aspirin had conflicting results, however, and lacked sufficient power to estimate major harms, such as gastrointestinal bleeding and hemorrhagic stroke (5, 6). Thus, the role of aspirin in primary prevention has remained controversial. The new USPSTF recommendation incorporates additional data from three recent trials and provides more reliable estimates of both benefits and harms of aspirin in patients without known heart disease.

Efficacy of Chemoprevention

Five trials have examined the effects of daily or every-other-day aspirin for the primary prevention of cardiovascular events over periods of 4 to 7 years (7–9). Most participants were men older than 50 years of age. Meta-analysis of pooled data from all of the studies showed that aspirin therapy reduced the risk for coronary heart disease by 28% (summary odds ratio, 0.72 [95% CI, 0.60 to 0.87]). Summary estimates showed no significant effects of aspirin on total mortality (odds ratio, 0.93 [CI, 0.84 to 1.02]) and stroke (odds ratio, 1.02 [CI, 0.85 to 1.23]).

Harms of Chemoprevention

These five primary prevention trials, and a larger number of randomized, controlled trials of secondary prevention that enrolled patients with heart disease or stroke, demonstrate that aspirin increases rates of gastrointestinal bleeding. Estimated rates of major gastrointestinal bleeding episodes are approximately 2 to 4 per

1000 middle-aged persons (4 to 12 per 1000 for older persons) given aspirin for 5 years (10–12).

These controlled trials in primary and secondary prevention settings also suggest that aspirin increases rates of hemorrhagic strokes by a small amount (0 to 2 per 1000 persons given aspirin for 5 years) (5–7). Such estimates are less reliable than those of gastrointestinal bleeding because few strokes were reported in the trials.

RECOMMENDATIONS OF OTHER ORGANIZATIONS

In 1994, the Canadian Task Force on Preventive Health Care concluded that the evidence was not strong enough to recommend for or against use of aspirin for primary prevention of heart disease in men or women and recommended that physicians and patients balance the reduced rate of nonfatal myocardial infarction against potential adverse effects (13). In 2000, the American Diabetes Association recommended that clinicians consider aspirin for primary prevention of heart disease in diabetic patients who are older than 30 years of age or have risk factors for cardiovascular disease and no contraindications to aspirin therapy (14). In 1997, the American Heart Association concluded that aspirin may be warranted for patients at high risk for myocardial infarction but that health care providers must consider a patient's particular cardiovascular risk profile, the demonstrated benefits of aspirin on reducing risk for a first myocardial infarction, and known and unknown side effects of aspirin (15). In 1998, the European Society of Cardiology recommended low-dose aspirin (75 mg) for patients with well-controlled hypertension and men at "particularly" high risk for coronary heart disease, but not for all persons at high risk (16).

APPENDIX

Members of the U.S. Preventive Services Task Force are Alfred O. Berg, MD, MPH, *Chair* (University of Washington, Seattle, Washington); Janet D. Allan, PhD, RN, CS, *Vice-Chair* (University of Texas Health Science Center, San Antonio, Texas); Paul S. Frame, MD (Tri-County Family Medicine, Cohocton, New York, and University of Rochester, Rochester, New York); Charles J. Homer, MD, MPH (National Initiative for Children's Healthcare Quality, Boston, Massachusetts); Mark S. Johnson, MD, MPH (University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey); Jonathan D. Klein, MD, MPH (University of Rochester School of Medicine, Rochester, New York); Tracy A. Lieu, MD, MPH (Harvard Pilgrim Health Care and Harvard Medical School, Boston, Massachusetts); Cynthia D. Mulrow, MD, MSc (University of Texas Health Science Center at San Antonio, Audie L. Murphy Memorial Veterans Hospital, San Antonio, Texas); C. Tracy Orleans, PhD (The Robert Wood Johnson Foundation, Princeton, New Jersey); Jeffrey F. Peipert, MD, MPH (Women and Infants' Hospital, Providence, Rhode Island); Nola J. Pender, PhD, RN (University of Michigan, Ann Arbor, Michigan); Albert L. Siu, MD, MSPH (Mount Sinai School of Medicine and The Mount Sinai Medical Center, New York, New York); Steven M. Teutsch, MD, MPH (Merck & Co., Inc., West Point, Penn-

Appendix Table 1. **U.S. Preventive Services Task Force Grades and Recommendations***

Grade	Recommendation
A	The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*
B	The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*
C	The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that the [service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

Appendix Table 2. **U.S. Preventive Services Task Force Grades for Strength of Overall Evidence***

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a three-point scale (good, fair, poor).

sylvania); Carolyn Westhoff, MD, MSc (Columbia University College of Physicians and Surgeons, New York, New York); and Steven H. Woolf, MD, MPH (Medical College of Virginia, Virginia Commonwealth University, Fairfax, Virginia).

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Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.ahrq.gov/clinic/uspstfix.htm) and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (800-358-9295).

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Aspirin for the Primary Prevention of Cardiovascular Events: A Summary of the Evidence for the U.S. Preventive Services Task Force

Michael Hayden, MD, MPH; Michael Pignone, MD, MPH; Christopher Phillips, MD, MPH; and Cynthia Mulrow, MD, MSc

Background: The use of aspirin to prevent cardiovascular disease events in patients without a history of cardiovascular disease is controversial.

Purpose: To examine the benefits and harms of aspirin chemoprevention.

Data Sources: MEDLINE (1966 to May 2001).

Study Selection: 1) Randomized trials at least 1 year in duration that examined aspirin chemoprevention in patients without previously known cardiovascular disease and 2) systematic reviews, recent trials, and observational studies that examined rates of hemorrhagic strokes and gastrointestinal bleeding secondary to aspirin use.

Data Extraction: One reviewer read and extracted data from each included article and constructed evidence tables. A second reviewer checked the accuracy of the data extraction. Discrepancies were resolved by consensus.

Data Synthesis: Meta-analysis was performed, and the quantitative results of the review were then used to model the consequences of treating patients with different levels of baseline risk for coronary heart disease. Five trials examined the effect of aspirin on cardiovascular events in patients with no previous cardiovascular disease. For patients similar to those enrolled in the trials, aspirin reduces the risk for the combined end point of nonfatal myocardial infarction and fatal coronary heart disease (summary odds ratio, 0.72 [95% CI, 0.60 to 0.87]). Aspirin increased the risk for hemorrhagic strokes (summary odds ratio, 1.4 [CI, 0.9 to 2.0]) and major gastrointestinal bleeding (summary odds ratio, 1.7 [CI, 1.4 to 2.1]). All-cause mortality (summary odds ratio, 0.93 [CI, 0.84 to 1.02]) was not significantly affected.

For 1000 patients with a 5% risk for coronary heart disease events over 5 years, aspirin would prevent 6 to 20 myocardial infarctions but would cause 0 to 2 hemorrhagic strokes and 2 to 4 major gastrointestinal bleeding events. For patients with a risk of 1% over 5 years, aspirin would prevent 1 to 4 myocardial infarctions but would cause 0 to 2 hemorrhagic strokes and 2 to 4 major gastrointestinal bleeding events.

Conclusions: The net benefit of aspirin increases with increasing cardiovascular risk. In the decision to use aspirin chemoprevention, the patient's cardiovascular risk and relative utility for the different clinical outcomes prevented or caused by aspirin use must be considered.

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See related article on pp 157-160 and editorial comment on pp 155-156.

Cardiovascular disease, including ischemic coronary heart disease, stroke, and peripheral vascular disease, is the leading cause of morbidity and death in the United States (1). In 1997, the age-adjusted mortality rate due to coronary heart disease, cerebrovascular disease, and atherosclerotic disease was 194 per 100 000 persons, which is equivalent to more than 500 000 deaths per year (1). The estimated direct and indirect costs of coronary heart disease and stroke were $145 billion for 1999 (2).

Although the benefit of aspirin for patients with known cardiovascular disease is well established (3), the question of whether aspirin reduces the risk for cardiovascular disease in persons without known cardiovascular disease is controversial. Two early randomized trials of aspirin in healthy men, the U.S. Physicians' Health Study (PHS) and the British Male Doctors' Trial (BMD), had conflicting results regarding whether aspirin reduced the risk for myocardial infarction. Neither trial had sufficient power to precisely estimate major harms, such as gastrointestinal bleeding and hemorrhagic stroke (4, 5).

The results of these randomized, controlled trials were available to the members of U.S. Preventive Services Task Force at the time of their 1996 recommendation (4, 5). At that time, the Task Force found insufficient evidence to recommend for or against routine aspirin prophylaxis for the primary prevention of myocardial infarction in asymptomatic persons (6). Two additional large primary prevention trials were published in 1998, and another was reported in January 2001 (7–9). In light of the new evidence, the U.S. Preventive

Table 1. **Summary of Primary Prevention Trials***

Variable	BMD	PHS	TPT	HOT	PPP
Reference	5	4	7	8	9
Year	1988	1989	1998	1998	2001
Location	United Kingdom	United States	United Kingdom	Worldwide	Italy
Duration of therapy, y†	5.8	5	6.8	3.8	3.6
Patients (women), *n*	5139 (0)	22 071 (0)	2540 (0)	18 790 (8831)	4495 (2583)
Aspirin dosage	500 mg/d	325 mg every other day	75 mg/d (controlled release)	75 mg/d	100 mg/d
Control	No placebo	Placebo	Placebo	Placebo	No placebo
Additional therapies	None	β-Carotene (50% of patients)	Warfarin‡	Felodipine with or without ACE inhibitor or β-blocker	Vitamin E
Included patients	Male physicians	Male physicians	Men at high risk for heart disease	Men and women with a diastolic blood pressure of 100 to 115 mm Hg	>1 major risk factor for CHD
Age	<60 y (46.9%); 60–69 y (39.3%); 70–79 y (13.9%)	Mean, 53 y (range, 40–84 y)	Mean, 57.5 y (range, 45–69 y)	Mean, 61.5 y (range, 50–80 y)	<60 y (29%); 60–69 y (45%); 70–79 y (24%)
Quality	Fair§	Good	Good	Good	Fair§

* ACE = angiotensin-converting enzyme; BMD = British Male Doctors' Trial; CHD = coronary heart disease; HOT = Hypertension Optimal Treatment Trial; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.
† Values given are means except for the TPT value, which is the median.
‡ Data from patients who received warfarin are not included in this table.
§ No placebo control or blinding.

Services Task Force sought to reassess the value of aspirin for the primary prevention of cardiovascular events. The Task Force's assessment was performed in partnership with the Agency for Healthcare Research and Quality, Rockville, Maryland, and investigators from the RTI-UNC Evidence-based Practice Center, Research Triangle Park, North Carolina. For this review, we examined three key questions: 1) Does aspirin chemoprevention in patients without known cardiovascular disease reduce the risk for myocardial infarction, stroke, and death? 2) Does aspirin chemoprevention increase major gastrointestinal bleeding, hemorrhagic strokes, or both? 3) What is the balance of benefits and harms for aspirin therapy in patients with different levels of risk for coronary heart disease? The analytic framework of the review can be found in **Appendix Figure 1** (available at www.annals.org).

METHODS

Identification of Relevant Trials

We searched MEDLINE from 1966 to May 2001 to identify studies examining aspirin's ability to prevent cardiovascular events and its likelihood of causing adverse effects. The literature search and data extraction are detailed in the Appendix (available at www.annals.org).

Quality Assessment

We assessed the quality of the trials that examined the benefits of aspirin therapy, considering methods of randomization, blinding, analysis by intention to treat, follow-up rates, and crossover of assigned interventions. To look for differences in estimates of effect, we then performed meta-analyses using only the trials considered to be of good quality.

Modeling

We used our best estimates of the beneficial and harmful effects of aspirin chemoprevention to model its impact on populations of patients with different levels of risk for coronary heart disease. We estimated beneficial effects by using the odds ratios calculated from the meta-analyses; estimates of harmful effects were derived from other systematic reviews, supplemented by studies identified in our literature searches. We based our estimates on 1000 persons receiving aspirin for 5 years and used 95% CIs from the meta-analyses to produce plausible ranges around our point estimates. We also examined how these effects may differ for elderly persons, women, and patients with hypertension or diabetes.

Statistical Analyses

For individual trials, we calculated estimates of unadjusted odds ratios with 95% CIs (10). Because not all of the trials presented their outcomes using the same means of categorization, we contacted the investigators in some cases to determine the actual numbers of certain events and recalculated summary measures to improve comparability. We performed meta-analysis using the DerSimonian and Laird random-effects model in RevMan (Cochrane Collaboration, Oxford, United Kingdom) (11). Heterogeneity was assessed by using graphs of the outcomes and the Mantel–Haenszel chi-square test.

DATA SYNTHESIS

Literature Searches

The results of our search strategy are shown in the Appendix (available at www.annals.org). We identified 5 randomized, controlled trials that had been designed to assess the efficacy of aspirin in the primary prevention of cardiovascular disease: the British Male Doctors' Trial (BMD), the Physicians' Health Study (PHS), the Thrombosis Prevention Trial (TPT), the Hypertension Optimal Treatment Trial (HOT), and the Primary Prevention Project (PPP) (4, 5, 7–9). We excluded 2 large trials that examined the effect of aspirin in patients with diabetes or with stable angina because more than 10% of the participants had definite or suspected vascular disease (12, 13). From our search for articles on adverse effects, we identified 9 articles that examined the effect of aspirin on gastrointestinal bleeding and hemorrhagic stroke (3, 14–21).

Trial Characteristics

The characteristics of the 5 randomized trials, which included a total of more than 50 000 patients, are shown in **Table 1**. The duration of the trials ranged from 3 to 7 years. Only 2 trials (HOT and PPP) included women. Aspirin dosage was 500 mg daily in BMD and 162 mg or less per day in the other 4 trials. Most participants were middle-aged, although 4 of the 5 trials included substantial numbers of patients who were 70 to 80 years of age.

Assessment of Study Quality

Overall, the quality of the trials examining the effectiveness of aspirin was high. All 5 trials concealed allocation of randomization. Researchers and participants were blinded in 3 trials (PHS, HOT, and TPT). In BMD and PPP, participants were not blinded and were not given placebo pills. Analyses in all trials were by intention to treat. Fewer than 1% of participants were lost to follow-up in BMD, PHS, and TPT, and 2.6% were lost to follow-up in HOT. In PPP, 7.7% of patients were lost to clinical follow-up, but data on vital status were obtained from census offices for 99.3% of the total sample.

During BMD, 39% of participants in the aspirin group discontinued therapy, primarily because of dyspepsia; 11% of participants assigned to no therapy began taking aspirin during the course of the trial. In contrast, in PHS, 14% of participants crossed over to the opposing treatment groups but rates of gastrointestinal discomfort did not differ significantly in each group. In PPP, 19% of patients assigned to aspirin discontinued taking it (8% due to side effects) and 7% of patients assigned to "no aspirin" were taking aspirin at the trial's conclusion. Crossover rates were not explicitly reported in TPT and HOT, although approximately 50% of patients participating in TPT withdrew for unreported reasons. However, the rate of withdrawal in TPT did not differ between the treatment and control groups. On the basis of these features, we rated the quality of

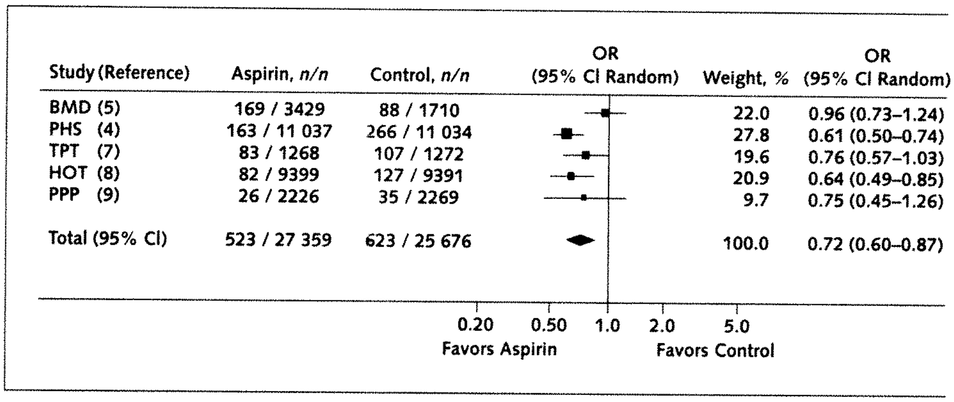
Table 2. **Effect of Aspirin on Risk for Coronary Heart Disease in Primary Prevention Trials***

Trial (Reference)	Aspirin Events/Patients	Control Events/Patients	Odds Ratio (95% CI)	Duration of Therapy†	Annual Risk for a CHD Event among Control Patients	Approximate Vascular Events Avoided per 1000 Patients Treated per Year
	n/n (%)			*y*	*%*	*n*
BMD (5)	169/3429 (4.93)	88/1710 (5.15)	0.96 (0.73–1.24)	5.8	0.89	0.4
PHS (4)	163/11 037 (1.48)	266/11 034 (2.41)	0.61 (0.50–0.74)	5	0.48	1.9
TPT (7)	83/1268 (6.55)	107/1272 (8.41)	0.76 (0.57–1.03)	6.8	1.24	2.7
HOT (8)	82/9399 (0.87)	127/9391 (1.35)	0.64 (0.49–0.85)	3.8	0.36	1.3
PPP (9)	26/2226 (1.17)	35/2269 (1.54)	0.75 (0.45–1.26)	3.6	0.43	1.0

* BMD = British Male Doctors' Trial; CHD = coronary heart disease; HOT = Hypertension Optimal Treatment Trial; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.

† Values given are means except for the TPT value, which is the median.

Figure 1. **Meta-analysis of total coronary heart disease events.**



Study (Reference)	Aspirin, *n/n*	Control, *n/n*	OR (95% CI Random)	Weight, %	OR (95% CI Random)
BMD (5)	169 / 3429	88 / 1710		22.0	0.96 (0.73–1.24)
PHS (4)	163 / 11 037	266 / 11 034		27.8	0.61 (0.50–0.74)
TPT (7)	83 / 1268	107 / 1272		19.6	0.76 (0.57–1.03)
HOT (8)	82 / 9399	127 / 9391		20.9	0.64 (0.49–0.85)
PPP (9)	26 / 2226	35 / 2269		9.7	0.75 (0.45–1.26)
Total (95% CI)	523 / 27 359	623 / 25 676		100.0	0.72 (0.60–0.87)

BMD = British Male Doctors' Trial; HOT = Hypertension Optimal Treatment Trial; OR = odds ratio; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial. The result of the chi-square test for heterogeneity was 8.07 ($P = 0.089$).

PHS, TPT, and HOT as "good" and the quality of BMD and PPP as "fair."

Effect of Aspirin on Coronary Heart Disease

All trials had point estimates suggesting that aspirin prevented total coronary heart disease events, defined as nonfatal myocardial infarction or death due to coronary heart disease (fatal myocardial infarction or sudden death) (**Table 2**). In PHS and TPT, aspirin use was associated with increases in sudden death that did not reach statistical significance: 22 events with aspirin versus 12 events with placebo in PHS (odds ratio, 1.83 [95% CI, 0.91 to 3.71]) (4), and 18 events with aspirin versus 11 with placebo in TPT (odds ratio, 1.65 [CI, 0.78 to 3.51]) (22).

Meta-analysis of the 5 trials for the combined outcome of confirmed nonfatal myocardial infarction or death from coronary heart disease produced a summary odds ratio of 0.72 (CI, 0.60 to 0.87) (**Figure 1**). The Mantel–Haenszel test suggested possible heterogeneity ($P = 0.089$), reflecting the anomalous result of BMD. In that study, no difference was found in the rate of myocardial infarction between the intervention and control groups.

Mortality data for coronary heart disease (fatal myocardial infarctions and sudden death) from HOT and PPP were not reported separately in the main papers but were obtained from the authors (Hannson L. Personal communication, 2000; Roncaglioni C. Personal communication, 2001). Of the 5 trials, only PHS reported a statistically significant decrease in risk with aspirin (odds ratio, 0.64 [CI, 0.42 to 0.99]). Cumulative mortality rates for coronary heart disease in the placebo group were low, ranging from 0.15% in HOT to 2.7% in BMD and TPT. Meta-analysis of the 5 trials found a summary odds ratio of 0.87 (CI, 0.70 to 1.09) (**Figure 2**, *top*). There was no significant heterogeneity in trial results ($P > 0.2$).

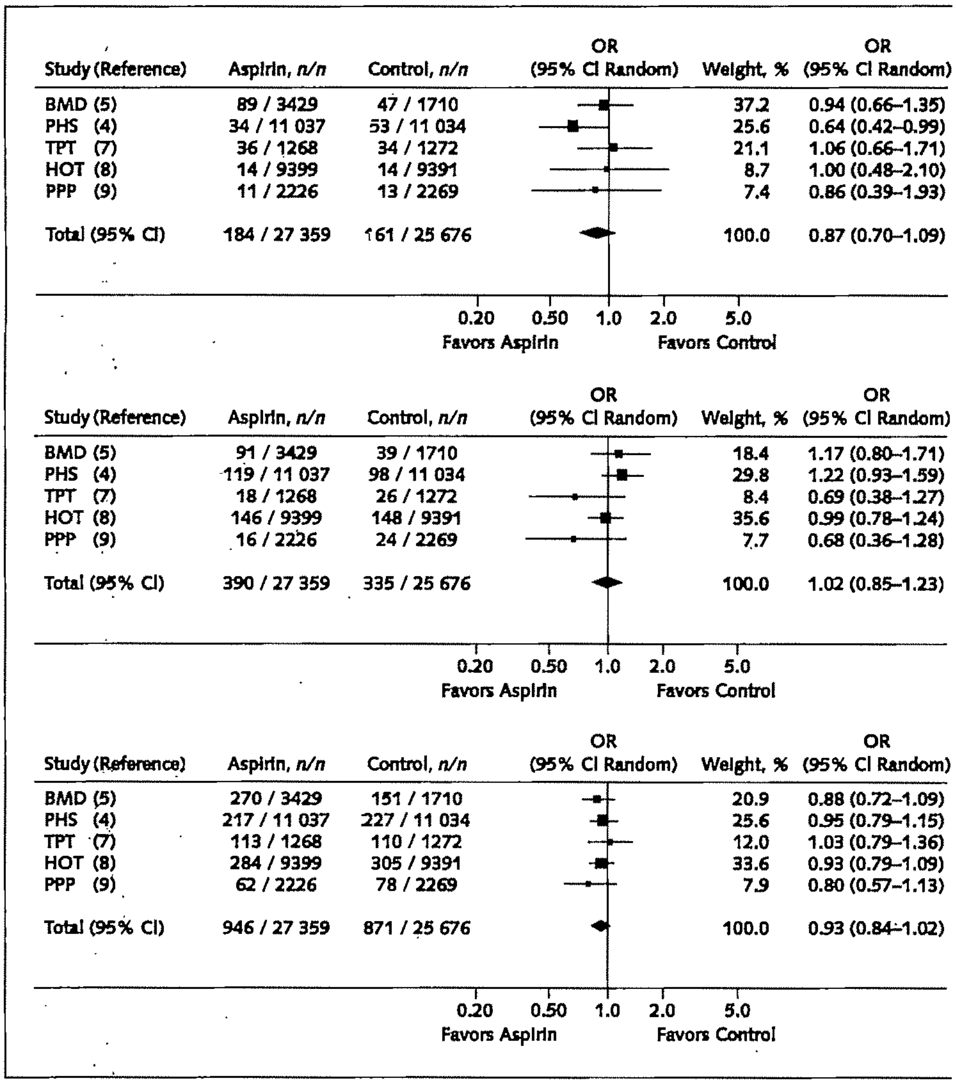
Effect of Aspirin on Stroke

It is difficult to interpret the overall effect of aspirin on stroke because the effect differs according to stroke subtype (**Table 3**). Data from secondary prevention trials suggest that aspirin prevents ischemic strokes but show that aspirin can also cause hemorrhagic stroke. The effect of aspirin on the total incidence of stroke depends on the patient's underlying risk for each stroke subtype (23). Overall stroke rates were lower than expected (based on age and risk factors) in all 5 primary prevention trials (**Table 4**). In each trial, control participants who had not been given aspirin had a less than 2% incidence of total strokes over 5 years. Because of the lower-than-expected stroke rates, the individual trials had limited statistical power to reliably detect the true effect of aspirin on stroke. Point estimates in PPP and TPT suggested modest decreases in total strokes, but CIs were wide (7, 23). In HOT, no effect of aspirin on overall rates of stroke was seen. In BMD and PHS, trends toward increased risk for stroke in aspirin-treated patients were observed but did not reach statistical significance (4, 5). The summary estimate (**Figure 2**, *middle*) showed no difference in total stroke overall (odds ratio, 1.02 [CI, 0.85 to 1.23]), and the results displayed no significant heterogeneity ($P > 0.2$).

The low number of strokes and the imperfect classification of stroke subtypes limited our ability to estimate the independent effect of aspirin on ischemic stroke in primary prevention settings. Rates of ischemic stroke were not specifically reported in HOT (8), and BMD did not use neuroimaging to differentiate ischemic from hemorrhagic strokes (5). In PHS, 91 ischemic strokes were seen with aspirin and 82 were seen with placebo (odds ratio, 1.11 [CI, 0.83 to 1.50]) (5). In TPT, 10 ischemic strokes occurred in the aspirin group and 18 occurred in the placebo group (odds ratio, 0.55 [CI, 0.25 to 1.20]) (7). Fourteen ischemic strokes in the intervention group and 21 in the "no aspirin" group were reported in PPP (9).

Despite the uncertainty of stroke classification, Hart and colleagues (19) combined data from the first 4 primary prevention trials (4, 5, 7, 8) and concluded that aspirin appeared to have no effect on ischemic strokes in

Figure 2. **Meta-analysis of the effect of aspirin on coronary heart disease mortality (*top*), fatal and nonfatal stroke events (*middle*), and all-cause mortality (*bottom*).**



Study (Reference)	Aspirin, *n/n*	Control, *n/n*	Weight, %	OR (95% CI Random)
BMD (5)	89 / 3429	47 / 1710	37.2	0.94 (0.66–1.35)
PHS (4)	34 / 11 037	53 / 11 034	25.6	0.64 (0.42–0.99)
TPT (7)	36 / 1268	34 / 1272	21.1	1.06 (0.66–1.71)
HOT (8)	14 / 9399	14 / 9391	8.7	1.00 (0.48–2.10)
PPP (9)	11 / 2226	13 / 2269	7.4	0.86 (0.39–1.93)
Total (95% CI)	184 / 27 359	161 / 25 676	100.0	0.87 (0.70–1.09)

Study (Reference)	Aspirin, *n/n*	Control, *n/n*	Weight, %	OR (95% CI Random)
BMD (5)	91 / 3429	39 / 1710	18.4	1.17 (0.80–1.71)
PHS (4)	119 / 11 037	98 / 11 034	29.8	1.22 (0.93–1.59)
TPT (7)	18 / 1268	26 / 1272	8.4	0.69 (0.38–1.27)
HOT (8)	146 / 9399	148 / 9391	35.6	0.99 (0.78–1.24)
PPP (9)	16 / 2226	24 / 2269	7.7	0.68 (0.36–1.28)
Total (95% CI)	390 / 27 359	335 / 25 676	100.0	1.02 (0.85–1.23)

Study (Reference)	Aspirin, *n/n*	Control, *n/n*	Weight, %	OR (95% CI Random)
BMD (5)	270 / 3429	151 / 1710	20.9	0.88 (0.72–1.09)
PHS (4)	217 / 11 037	227 / 11 034	25.6	0.95 (0.79–1.15)
TPT (7)	113 / 1268	110 / 1272	12.0	1.03 (0.79–1.36)
HOT (8)	284 / 9399	305 / 9391	33.6	0.93 (0.79–1.09)
PPP (9)	62 / 2226	78 / 2269	7.9	0.80 (0.57–1.13)
Total (95% CI)	946 / 27 359	871 / 25 676	100.0	0.93 (0.84–1.02)

Results of the chi-square test for heterogeneity were 2.96 for coronary heart disease mortality, 5.36 for fatal and nonfatal stroke events, and 1.58 for all-cause mortality ($P > 0.2$ in all cases). BMD = British Male Doctors' Trial; HOT = Hypertension Optimal Treatment Trial; OR = odds ratio; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.

Table 3. **Estimates of the Role of Aspirin in Primary Prevention of Total Fatal and Nonfatal Stroke***

Trial (Reference)	Aspirin Events/Patients	Control Events/Patients	Odds Ratio (95% CI)	Duration of Therapy†	Annual Risk for Stroke among Control Patients	Vascular Events Avoided per 1000 Patients Treated per Year	Vascular Events Caused per 1000 Patients Treated per Year
	n/n (%)			*y*	*%*	*n*	
BMD (5)	91/3429 (2.65)	39/1710 (2.28)	1.17 (0.80–1.71)	5.8	0.39	–	0.6
PHS (4)	119/11 037 (1.08)	98/11 034 (0.89)	1.22 (0.93–1.59)	5	0.18	–	0.4
TPT (7)	18/1268 (1.42)	26/1272 (2.04)	0.69 (0.38–1.27)	6.8	0.30	0.9	–
HOT (8)	146/9399 (1.55)	148/9391 (1.58)	0.99 (0.78–1.24)	3.8	0.41	0.1	–
PPP (9)	16/2226 (0.72)	24/2269 (1.06)	0.68 (0.36–1.28)	3.6	0.29	0.9	–

* BMD = British Male Doctors' Trial; HOT = Hypertension Optimal Treatment Trial; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.

† Values given are means except for the TPT value, which is the median.

the middle-aged, relatively low-risk patients (relative risk, 1.03 [CI, 0.87 to 1.21]) (19).

Effect of Aspirin on All-Cause Mortality

None of the 5 trials found significant differences between aspirin-treated and control groups for all-cause mortality rates. Five-year mortality rates in the control groups of the individual trials ranged from 2% to 10%. The summary odds ratio for the effect of aspirin on all-cause mortality was 0.93 (CI, 0.84 to 1.02), consistent with a small or no reduction in all-cause mortality over 3 to 7 years (**Figure 2**, *bottom*).

Effectiveness of Aspirin Chemoprevention in Patient Subgroups

Most of the participants in the 5 randomized trials were middle-aged men. Limited data are available to examine whether the effect of aspirin differs in other demographic groups, including elderly persons, women, and persons with diabetes or hypertension. The following data come primarily from subgroup analyses and should be interpreted with caution.

Age

In PHS, aspirin reduced the relative risk for myocardial infarction for patients 70 to 84 years of age (relative risk, 0.49) as much as or more than it did for patients 60 to 69 years of age (relative risk, 0.46) and patients 50 to 59 years of age (relative risk, 0.58). In HOT, aspirin's effectiveness in patients older than 65 years of age (30% of the study sample) did not differ from its effect in those 50 to 64 years of age (24). In TPT, however, patients 65 to 69 years of age did not benefit from aspirin (relative risk, 1.12) but younger patients did. Relative risks were 0.75 for patients 50 to 59 years of age and 0.61 for patients 60 to 64 years of age.

Sex

Only 2 of the 5 primary prevention trials included women (HOT and PPP). Kjeldsen and coworkers (24) performed a subgroup analysis of HOT to examine the influence of patient sex on the effectiveness of aspirin chemoprevention. Aspirin reduced the incidence of myocardial infarction in men (2.9/1000 patient-years in the aspirin group vs. 5/1000 patient-years in controls; relative risk, 0.58 [CI, 0.41 to 0.81]). However, its effect in women was smaller and not statistically significant (1.7/1000 person-years in the aspirin group vs. 2.1/1000 patient-years in controls; relative risk, 0.81 [CI, 0.49 to 1.31]). Sex differences in the effect of aspirin were not seen for stroke or all-cause mortality. In PPP, the investigators noted that women seemed to derive the same level of benefit from reduction of coronary heart disease as men, but specific data were not presented.

The question of whether sex modifies the effect of aspirin remains unclear. The Women's Health Study, a primary prevention trial that will test low-dose aspirin in approximately 40 000 patients, is expected to clarify risks and benefits among women (10).

Patients with Diabetes Mellitus

The proportion of patients with diabetes mellitus was small in each trial (PPP, 17%; HOT, 8%; PHS, 2%; BMD, 2%; TPT, 2%). In PHS, patients with diabetes derived greater benefit from aspirin than those without diabetes (relative risk, 0.39 vs. 0.60). Pooled data from aspirin trials in secondary prevention settings (23) and a single trial in diabetic patients with and without coronary heart disease (12) also suggested that diabetic patients benefit as much or more from aspirin as nondiabetic patients.

Patients with Hypertension

The influence of hypertension on the effectiveness of aspirin chemoprevention has been examined in subgroup analyses. In TPT, Meade and Brennan (22) found that aspirin reduced total cardiovascular events in patients whose systolic blood pressure was less than 130 mm Hg (relative risk, 0.59) but not in patients whose systolic blood pressure was greater than 145 mm Hg (relative risk, 1.08). Patients with systolic blood pressure between 130 and 145 mm Hg also had reduced risk (relative risk, 0.68). In PHS, patients who were taking aspirin and had systolic blood pressure greater than 150 mm Hg had a relative risk of 0.65 for myocardial infarction, compared with relative risks of 0.55 for those with systolic blood pressure between 130 and 149 mm Hg and 0.52 for those with systolic blood pressure between 110 and 129 mm Hg (4). Significant reductions in coronary heart disease events were seen in HOT among patients with treated hypertension, but HOT did not have a comparison group of patients without hypertension (8).

On the basis of these data, aspirin seems to reduce risk for coronary heart disease in patients with treated hypertension, but its effects may be attenuated in patients with poorly controlled blood pressure.

Effect of Study Quality on Effectiveness of Aspirin

We performed an additional set of meta-analyses using only the 3 trials we rated as good (PHS, TPT, HOT). The reduction in total coronary heart disease events was slightly larger (summary odds ratio, 0.65 [CI, 0.56 to 0.75]), but other outcomes were similar to our main analysis.

Adverse Effects of Aspirin Therapy

Hemorrhagic Stroke

The event rates for hemorrhagic strokes, including intracranial hemorrhage, were higher among aspirin-exposed participants than controls in BMD, PHS, and TPT, although these differences did not reach statistical significance in any single trial (Table 4) (4, 5, 7). In BMD, most strokes (>60%) were of unknown cause because computed tomography was not performed in most cases (5). In HOT and PPP, hemorrhagic strokes were almost equally common in the intervention and control groups (8, 9).

Two systematic reviews and meta-analyses have examined the effect of aspirin on the incidence of hemorrhagic stroke in the primary prevention trials. Hart and colleagues (19) pooled the results of the first 4 primary prevention studies and estimated that the relative risk for hemorrhagic stroke due to long-term aspirin use was 1.36 (CI, 0.88 to 2.1). Sudlow (25) recently performed a similar analysis using all 5 trials and reached a similar effect estimate (odds ratio, 1.4 [CI, 0.9 to 2.0]). In this analysis, the estimated annual excess risk with aspirin was 0.1 event per 1000 users.

He and coworkers (3) performed a meta-analysis of 16 trials (14 secondary prevention trials and the 2 older primary prevention trials [BMD and PHS]) that reported stroke subtype. Taken together, the trials involved more than 55 000 participants. Participants had a mean age of 59 years, and 86% were men. The mean

Table 4. **Estimates of the Role of Aspirin in Hemorrhagic Stroke and Intracranial Hemorrhage***

Trial (Reference)	Aspirin Events/Patients	Control Events/Patients	Odds Ratio (95% CI)	Duration of Therapy	Annual Approximate Control Group Risk	Approximate Excess Bleeding Events per 1000 Patients Treated per Year	Approximate Bleeding Events Avoided per 1000 Patients Treated per Year
	n/n (%)			y	%	n	
BMD (5)	13/3429 (0.38)	6/1710 (0.35)	1.08 (0.41–2.85)	5.8	0.06	0.05	–
PHS (4)	23/11 037 (0.21)	12/11 034 (0.11)	1.92 (0.95–3.86)	5	0.02	0.2	–
TPT (7)	3/1268 (0.24)	2/1272 (0.16)	1.51 (0.25–9.03)	6.8	0.02	0.12	–
HOT (8)	14/9399 (0.15)	15/9391 (0.16)	0.93 (0.45–1.93)	3.8	0.04	–	0.03
PPP (9)	2/2226 (0.08)	3/2269 (0.13)	0.67 (NR)	3.6	0.04	–	0.12

* BMD = British Male Doctors' Trial; HOT = Hypertension Optimal Treatment Trial; NR = not reported; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.

Table 5. **Estimates of the Role of Aspirin in Gastrointestinal Bleeding***

Trial (Reference)	Type of Gastrointestinal Bleeding	Cumulative Incidence		*P* Value	Excess Bleeding Events per 1000 Patients Treated per Year	Fatal Gastrointestinal Bleeding Events	
		Aspirin Group	Control Group			Aspirin Group	Control Group
		%			←	*n*	→
BMD (5)	Self-reported peptic ulcer disease	2.6	1.6	<0.05	1.7	3	3
PHS (4)	Upper gastrointestinal ulcers	1.5	1.3	0.08	0.4	1	0
TPT (7)	Major or intermediate bleeding†	1.7	0.8	NR	1.3	0	1
HOT (8)	Fatal and nonfatal major gastrointestinal bleeding events‡	0.8	0.4	NR	1.1	5	3
PPP (9)	Gastrointestinal bleeding§	0.8	0.2	NR	1.5	0	0

* BMD = British Male Doctors' Trial; HOT = Hypertension Optimal Treatment Trial; NR = not reported; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.

† Major bleeding included fatal and life-threatening hemorrhages that required transfusion, surgery, or both. Intermediate episodes were bleeding events that prompted patients to notify research coordinators separately from routine questionnaires.

‡ Major bleeding was not defined.

§ Described as severe but nonfatal.

dosage of aspirin was 273 mg/d, and the mean duration of treatment was 37 months. The summary relative risk for hemorrhagic stroke with aspirin use was 1.84 (CI, 1.24 to 2.74). He and coworkers estimated that aspirin increased the absolute risk for hemorrhagic stroke by 12 events (CI, 5 to 20 events) per 10 000 persons over approximately 3 years, or about 0.4 excess event per 1000 users annually. This estimate is higher than that in Sudlow's meta-analysis, which included only primary prevention trials. He and coworkers also concluded that the absolute risk for hemorrhagic stroke did not vary significantly according to preexisting cardiovascular disease, mean age, sample size, dosage of aspirin, or study duration, although the statistical power to detect such differences was low because of the small number of total events.

The small number of primary prevention trials makes it difficult to examine the influence of other factors on the relationship between aspirin and hemorrhagic stroke. He and coworkers' systematic review did not find that age was an independent predictor of risk for hemorrhagic stroke, but the power of the review to detect such differences was low. In the large Stroke Prevention in Atrial Fibrillation II trial (26), advanced age was associated with an increased incidence of bleeding during aspirin therapy in patients with atrial fibrillation. The rate of intracranial hemorrhage with aspirin use was 0.2% per year in patients 75 years of age or younger and 0.8% per year in patients older than 75 years of age.

The question of whether there is a "safe" dose of aspirin with respect to hemorrhagic stroke has been addressed only in observational studies. A case–control study from Australia (27) examined the relationship between the use of aspirin or other nonsteroidal anti-inflammatory medications and the risk for hemorrhagic stroke. Reported use of low-dosage aspirin (<1225 mg/wk) was not associated with an increased risk for hemorrhagic stroke (odds ratio, 1.00 [CI, 0.60 to 1.66]) in multivariate risk-adjusted analyses. Larger amounts of aspirin were associated with hemorrhagic stroke (odds ratio, 3.05 [CI, 1.02 to 9.14]).

Gastrointestinal Bleeding

Aspirin increased the rates of gastrointestinal bleeding in all 5 primary prevention trials. Detection of events, definition of a "significant" bleeding event, and reporting of location of upper gastrointestinal bleeding varied across trials (**Table 5**).

Pooling the data on major extracranial bleeding from the 5 primary prevention trials, Sudlow estimated that aspirin increased the risk for major extracranial bleeding (odds ratio, 1.7 [CI, 1.4 to 2.1]). This translates to an excess risk for major, mostly gastrointestinal bleeding events of 0.7 (CI, 0.4 to 0.9) per 1000 patients treated with aspirin per year (25).

Several other systematic reviews have examined the risk for gastrointestinal bleeding with aspirin use (14–16, 28). Roderick and associates (15) performed a systematic review of 21 trials from the Antiplatelet Trialists' Collaboration (1990), all but 1 of which were secondary prevention studies. They estimated pooled odds ratios of 1.5 to 2.0 for gastrointestinal bleeding due to aspirin. The risk for bleeding was greater in trials that used dosages exceeding 300 mg/d than in trials using lower dosages, but the difference was not statistically significant. Dickinson and Prentice (14) updated the Roderick review using data from trials that lasted more than 1 month. They determined that ongoing use of aspirin would produce an excess of two major gastrointestinal bleeding events per 1000 patient-years of exposure.

Recently, Derry and Loke (28) performed a systematic review and meta-analysis of trials published through 1999 that examined the risk for gastrointestinal hemorrhage with long-term (>1 year) aspirin use. They identified 24 randomized trials with a total of 66 000 participants and an average duration of 28 months. Aspirin use increased the odds of gastrointestinal hemorrhage (summary odds ratio, 1.68 [CI, 1.51 to 1.88]). The absolute risk difference was 1.05%. The authors estimated that treating 106 patients with aspirin for 28 months would lead to one excess episode of hemorrhage. Stalnikowicz-Darvasi performed a meta-analysis of 9 trials of low-dose aspirin prevention that had lasted at least 3 months (16); the pooled odds ratio for all gastrointestinal bleeding was 1.5 (CI, 1.3 to 1.7).

Derry and Loke (28) used meta-regression to examine the effect of aspirin dosage on the incidence of gastrointestinal hemorrhage and did not detect a statistically significant relationship (odds ratio, 1.015 [CI, 0.984 to 1.047] per 100-mg change in dose; $P > 0.2$). Cappelleri and colleagues (17) performed a meta-analysis and meta-regression to determine the effect of dosage on the risk for gastrointestinal bleeding with aspirin use among persons at high risk for vascular disease. They did not find a relationship between aspirin dose and risk for gastrointestinal bleeding but concluded that the likelihood of other gastrointestinal symptoms (for example, dyspepsia) increased with higher aspirin doses.

In a case–control study in Great Britain, Weil and coworkers (20) found that the risk for gastrointestinal bleeding was greater with all doses of aspirin compared with no usage but was higher with larger doses (odds ratios, 2.3 for 75 mg/d vs. 3.9 for 300 mg/d). Kelly and associates (18), in another case–control study, found an estimated relative odds of 2.6 for dosages less than 325 mg/d and 5.8 for larger doses. Enteric-coated or buffered preparations did not seem to reduce risk. Concomitant use of other nonsteroidal anti-inflammatory agents or anticoagulants further increased risk.

Table 6. **Summary Estimates of the Effect of Aspirin***

Outcome	Odds Ratio (95% CI)
Benefits	
Myocardial infarction	0.72 (0.60–0.87)
CHD death	0.87 (0.70–1.09)
Total stroke	1.02 (0.85–1.23)
All-cause mortality	0.93 (0.84–1.02)
Harms	
Hemorrhagic stroke	1.4 (0.9–2.0)
Major gastrointestinal bleeding event	1.7 (1.4–2.1)

* CHD = coronary heart disease.

Silagy and colleagues (21) examined the adverse effects of low-dosage aspirin (100 mg/d) in a randomized, double-blind, placebo-controlled trial of 400 patients older than 70 years of age who did not have preexisting vascular disease. The reported absolute rate of any gastrointestinal bleeding in the aspirin group was 3% after 1 year. One case of bleeding duodenal ulcer required hospitalization for transfusion and emergency surgery. No gastrointestinal bleeding was reported for patients in the control group. Existing meta-analyses have not determined (3) or have not examined (28) whether age modifies the effect of aspirin on gastrointestinal hemorrhage, although cohort data suggest that the absolute risk for bleeding is higher in elderly persons (26).

Gastrointestinal Bleeding: Summary

Aspirin chemoprevention, even at low doses, seems to increase the risk for gastrointestinal bleeding by a factor of 1.5 to 2. The absolute excess risk for major bleeding events appears to be approximately 3 per 1000 middle-aged men receiving low-dose aspirin for more than 5 years. Higher rates (up to 2/1000 persons per year) are likely in elderly patients and perhaps among those using higher doses of aspirin.

Modeling a Risk Threshold for Aspirin Chemoprevention

Table 6 presents a summary of the effect estimates for the most important outcomes related to aspirin use. The estimates are based on the results of meta-analyses of data from the 5 primary prevention trials and therefore are most valid for middle-aged men (50 to 65 years of age) taking low-dosage aspirin (≤162 mg/d).

We used our best estimates of the beneficial and harmful effects of aspirin chemoprevention to model its impact on populations of patients with different levels of

Table 7. **Estimated Benefits and Harms of Aspirin Therapy for Patients at Different Levels of Risk for Coronary Heart Disease Events***

Outcome	Estimated 5-Year Risk for CHD Events at Baseline		
	1%	3%	5%
Effect on all-cause mortality	No change	No change	No change
CHD events avoided, *n*	3 (1–4)	8 (4–12)	14 (6–20)
Ischemic strokes avoided, *n*	0	0	0
Hemorrhagic strokes precipitated, *n*	1 (0–2)	1 (0–2)	1 (0–2)
Major gastrointestinal bleeding events precipitated, *n*	3 (2–4)	3 (2–4)	3 (2–4)

* Estimates based on 1000 patients receiving aspirin for 5 years and a relative risk reduction of 28% for coronary heart disease (CHD) events in those who received aspirin. CHD events = nonfatal acute myocardial infarction, fatal CHD. Values in parentheses are 95% CIs. The following caveats apply to these estimates. 1) Reduction in CHD risk may be smaller in women, but data are limited. 2) For elderly persons, absolute risk for hemorrhagic stroke and major gastrointestinal bleeding may be two to three times higher in patients receiving aspirin; however, aspirin may provide benefit in elderly persons by reducing ischemic stroke, the incidence of which increases with age. Aspirin does not appear to improve incidence of ischemic stroke in middle-aged patients. 3) Risk for hemorrhagic stroke may be greater with larger doses of aspirin. 4) Aspirin may not prevent myocardial infarction in patients with uncontrolled hypertension (systolic blood pressure > 150 mm Hg). 5) Long-term outcomes (>5–7 years) are unknown. 6) Patients at high risk (≥10% 5-year risk) may derive greater benefit from aspirin, including a 15% to 20% reduction in ischemic stroke and all-cause mortality, because their risk is similar to that of patients with known CHD.

risk for coronary heart disease over 5 years. **Table 7** shows the net impact of low-dose aspirin chemoprevention on patients with different levels of risk. Treating patients with a moderately high risk (a 5-year risk of 5%) would prevent 14 events (range, 6 to 20). In low-risk patients, such as those with a 5-year risk of 1%, aspirin would prevent 3 events (range, 1 to 4). Low-dose aspirin is estimated to result in an excess of 1 hemorrhagic stroke (range, 0 to 2) and 3 major gastrointestinal bleeding events (range, 2 to 4) among 1000 persons treated in each group, independent of risk for coronary heart disease.

DISCUSSION

For patients without known cardiovascular disease who are similar to those enrolled in the 5 large primary prevention trials, our systematic review suggests that aspirin chemoprevention reduces myocardial infarction but has no effect on ischemic stroke or all-cause mortality over 5 years. Aspirin therapy also increases the risk for gastrointestinal bleeding and hemorrhagic stroke. Aspirin chemoprevention is probably beneficial for patients who have no previous diagnosis of cardiovascular disease but are at high risk for developing coronary heart disease in the next 5 years. Conversely, patients at low risk for coronary heart disease probably do not benefit from and may even be harmed by aspirin because the risk for adverse events may exceed the benefits of chemoprevention (6, 29).

To aid in applying these general results to individual patients, we have attempted to define quantitatively the benefits and harms of aspirin at various levels of risk for coronary heart disease. The advantage of such an approach is that it allows a more specific and accurate discussion and consideration of the potential consequences of using or not using aspirin for each individual patient.

Utilization of our results in shared decision making with patients requires an estimation of a given patient's absolute risk for coronary heart disease as well as his or her willingness to accept the risks of low-dose aspirin to avoid coronary heart disease. Risk for future coronary heart disease events can be predicted from coronary risk algorithms (30). Factors used to estimate risk include sex, age, blood pressure, serum total cholesterol level (or low-density lipoprotein cholesterol level), high-density lipoprotein cholesterol level, diabetes mellitus, cigarette smoking, and left ventricular hypertrophy. Several easy-to-use risk assessment tools, most based on risk equations derived from the Framingham Heart Study, are available on the Internet (for example, at www.intmed.mcw.edu/clincalc/heartrisk.html) or in printed form (30). Some tools calculate only 10-year risk estimates; in these cases, half of the 10-year estimate is a reasonable approximation of the 5-year risk for which we project our potential outcomes. Framingham data have recently been shown to generalize adequately to other populations (31). We have also provided a risk calculator at www.med-decisions.com to facilitate risk calculation.

Estimates of benefits and harms should be interpreted and compared cautiously. The principal beneficial effect of aspirin, a reduction in nonfatal myocardial infarction, cannot be directly equated to an adverse event, such as a stroke or gastrointestinal bleeding. We modeled outcomes over a period of 5 years because the trials included in our review ranged from 3 to 7 years in duration. However, outcomes from the use of aspirin chemoprevention will affect not only patients' current health status but also their future risk for coronary heart disease. For example, a nonfatal myocardial infarction may produce a relatively small decrement in the patient's current health status but may also increase the future risk for a more disabling condition, such as recurrent myocardial infarction or congestive heart failure, and may lead to premature death.

The value that individual patients place on the outcomes affected by aspirin will vary. Decision analysts have measured mean values in representative populations. Augustovski and associates (32) used existing studies to estimate utility values as follows: nonfatal myocardial infarction, 0.88; disabling stroke, 0.50; nondisabling stroke, 0.75; and gastrointestinal bleeding, 0.97. Our estimates of expected event rates and these mean utility values can provide an initial framework for discussion with individual patients, who may weigh or value outcomes differently.

Others have attempted to quantitate the benefits and harms of aspirin therapy (19, 33). Sanmuganathan and colleagues (34) performed a meta-analysis of the first four primary prevention trials and reached similar estimates of the beneficial effects of aspirin. In their analysis, they combined data on harms into a single category of "major bleeding events" induced, and they calculated that the number of bleeding events induced equaled the number of cardiovascular events averted when the cardiovascular event rate was 0.22% per year. They further estimated that the upper end of the 95% confidence interval for this point estimate occurred at an event rate of 0.8% per year for cardiovascular disease; this is equivalent to an event rate of 0.6% per year for coronary heart disease. Sanmuganathan and colleagues concluded that aspirin was "safe and worthwhile" for persons whose risk for coronary heart disease events exceeded 1.5% per year and was "unsafe" for persons whose risk was less than 0.5% per year. However, their analysis treated the beneficial and harmful outcomes as equal in magnitude, an assumption that oversimplifies the clinical dilemma.

Augustovski and associates (32) used a Markov decision analysis model to consider the effect of low-dose aspirin for primary prevention in patients with different risk factor profiles. Effect estimates were based on the evidence available at the time of the analysis, which was before publication of the three most recent trials. Outcomes were measured as changes in quality-adjusted life-days. For 55-year-old patients, those at low risk (0 risk factors in men; 0 or 1 risk factor in women) were harmed by aspirin therapy, whereas those at moderate to high risk (≥2 risk factors) seemed to benefit. However, because outcomes were presented in mean life-days gained or lost, it is difficult to translate their findings for use in counseling of individual patients.

On the basis of our review, we conclude that aspirin appears to reduce myocardial infarction but increases gastrointestinal and intracranial bleeding. The net effect of aspirin improves with increasing risk for coronary heart disease. Consideration of underlying risk for coronary heart disease, as well as the relative values patients attach to the main outcomes, can help patients and providers decide whether aspirin chemoprevention is warranted.

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LETTERS

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Prevention of Antibiotic Resistance in Hospitals

TO THE EDITOR: Kollef and Fraser (1) discussed adverse clinical outcomes associated with infections caused by antibiotic-resistant organisms. A factor other than unwitting undertreatment and enhanced virulence that may contribute significantly to such outcomes is the underlying status of the host. Many of the characteristics that predict acquisition of an antibiotic-resistant infection, such as prolonged hospital stay or prior receipt of antibiotics (for a previous infection), are markers for sicker hosts and hence themselves predict poor outcomes even in the absence of an antibiotic-resistant pathogen. Because patients cannot be randomly assigned to infection with a susceptible versus a resistant pathogen, confounding by underlying population differences is always a problem in comparative cohort or case–control studies in this field.

Adjustment for host characteristics that are known to predict clinical outcomes is essential in such studies, and even with such adjustment the possibility that unmeasured host characteristics rather than antibiotic resistance account for some or all of the observed outcome differences cannot be excluded. In many instances, patients who are infected by resistant pathogens seem to die with, rather than of, their infection.

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Reference

1. Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. Ann Intern Med. 2001;134:298-314. [PMID: 11182841]

TO THE EDITOR: In their superb review on antibiotic resistance in the intensive care unit (1), Drs. Kollef and Fraser incorrectly defined our approach to nosocomial pulmonary infiltrates. We did not quantitate the risk for nosocomial pneumonia but used a scoring system merely as an operational criterion for decision making about antibiotic therapy, regardless of whether patients had nosocomial pneumonia (2). Patients who had low clinical pulmonary infection scores (and were unlikely to have bacterial pneumonia) were randomly assigned to standard therapy, usually defined as multiple antibiotics for 10 or more days, or monotherapy for 3 days. Our approach, regardless of the precise definition or presence of nosocomial pneumonia, was associated with a significantly lower risk for antimicrobial resistance and superinfections and did not adversely affect length of stay or mortality.

Drs. Kollef and Fraser proposed many administrative approaches to curtail antibiotic resistance in the intensive care unit. Such strategies have largely been ineffective in altering prescribing habits of physicians. During our study, after realizing that their standard antibiotic practices were causing measurable harm to their patients, physicians voluntarily decreased antibiotic usage in the intensive care unit. This type of strategy is more likely to lead to enduring changes in antibiotic prescribing than imposed regulations.

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IN RESPONSE: Dr. Fraser and I agree with Dr. Johnson that patients' underlying host defenses play a very important role in determining susceptibility to infection with antibiotic-resistant microorganisms. In addition, studies attempting to define the impact of antibiotic resistance on clinical outcomes need to take severity of illness and other underlying patient characteristics into account. Only in this way can accurate estimates be made concerning the impact of antibiotic resistance on hospital mortality and other clinical outcomes. We also thank Drs. Singh and Yu for clarifying how they used the clinical pulmonary infection score in their clinical trial. More studies that define optimal management practices for the use of antibiotics among hospitalized patients are needed. These studies must define the costs and benefits of antibiotic exposure, as well as the potential harm caused by increasing the burden of antibiotic-resistant microorganisms in the hospital setting.

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Viral Pneumonia as a Serious Complication of Etanercept Therapy

TO THE EDITOR: Levels of tumor necrosis factor are elevated in the synovial fluid of patients with rheumatoid arthritis. Etanercept inhibits tumor necrosis factor and is an effective treatment for rheumatoid arthritis (1, 2). Tumor necrosis factor is also integral to the immune response to many pathogens, including respiratory viruses (3). We report a case of severe parainfluenza pneumonia in a patient taking etanercept.

A 54-year-old woman with severe rheumatoid arthritis presented with 10 days of dyspnea, pharyngitis, and headache. Examination revealed mild respiratory distress, fever (body temperature, 83 °C), and evidence of chronic rheumatoid arthritis and long-term steroid use. She had diffuse rales and a moderate holosystolic murmur (she had known aortic insufficiency). The leukocyte count was 5.1×10^9 cells/L, and studies of arterial blood revealed a pH of 7.45, $P\text{CO}_2$ of 35 mm Hg, and $P\text{O}_2$ of 68 mm Hg. Chest radiography showed a diffuse reticulonodular pulmonary pattern. The patient was hospitalized, and erythromycin and ceftriaxone were empirically administered.

Bacterial cultures of blood and sputum were nondiagnostic. Respiratory status worsened, requiring mechanical ventilation. A direct fluorescent antibody assay (Bartels Viral Respiratory Screening and Identification Kit, Medvet Diagnostics, Thebarton, South Australia, Australia) revealed parainfluenza virus type 3. Although ribavirin was not administered, the patient's condition improved and she was discharged on day 21.

Tumor necrosis factor may be particularly important in the immune response to some respiratory viruses (3). By inhibiting tumor necrosis factor, etanercept may allow benign respiratory viral infections to progress. In fact, clinical etanercept trials demonstrate a trend of increased respiratory infections in the treatment groups (1, 2, 4, 5) (**Table**). However, these studies may not have been sufficiently powered to demonstrate a difference in this outcome because of their relatively small sample sizes. We conclude that patients being treated with etanercept may benefit from close monitoring for symptoms of upper respiratory tract infections and that discontinuation of therapy may be indicated during viral respiratory syndromes. Further study of the relationship between etanercept therapy and respiratory viral infections may be warranted.

Table. **Respiratory Tract Infections or Rhinitis Reported in Four Studies of Etanercept Therapy in Patients with Rheumatoid Arthritis***

Study (Reference)	Placebo	Etanercept, 10 mg	Etanercept, 25 mg
Bathon et al. (1)	No placebo group	57 URTIs in 208 patients (27%)	72 URTIs in 207 patients (35%)
Moreland et al. (2)	URTI in 16% of 80 patients (0.93 event per patient-year)	URTI in 29% of 76 patients (0.85 event per patient-year)	URTI in 33% of 78 patients (1.11 events per patient-year)
Mease et al. (4)	4 RTIs in 30 patients (13%)	No 10-mg group	8 RTIs in 30 patients (27%)
Weinblatt et al. (5)	3% of 30 patients had rhinitis	No 10-mg group	14% of 59 patients had rhinitis

*RTI = respiratory tract infection; URTI = upper respiratory tract infection.

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Abuse of Epinephrine as a Stimulant

TO THE EDITOR: New forms of drug abuse are regularly reported, but the use of catecholamines appears to be unusual (1). We report an attempt to obtain stimulant effects through intravenous epinephrine injection.

A 33-year-old man was discovered by a nurse in the bathroom of a small hospital. He was lying on the floor with an empty syringe nearby. He was conscious, with tremors and a Glasgow coma score of 14. His heart rate was 150 beats/min on the electrocardiographic monitor, but no pulse was detected. Twenty minutes later, on physician arrival, the patient was conscious, with an arterial blood pressure of 80/45 mm Hg, a heart rate of 70 beats/min, and a respiratory rate of 12 breaths/min. Findings on clinical examination and results of electrocardiography were normal. The patient explained that he had achieved a satisfactory psychostimulant effect the previous day by experimenting with an intravenous injection of 0.5 mg of epinephrine in association with oxazepam ingestion. On this second attempt, he had injected 1 mg of epinephrine. He had planned to inject dobutamine as well but could not because of tremors. He was admitted to the emergency department for observation, and his course was uneventful, resulting in discharge a few hours later.

Stimulant abuse is common, but catecholamine use to obtain a stimulant effect is infrequent (1–3). To our knowledge, in previous reported cases, epinephrine overdose has uniformly been accidental or iatrogenic (1, 2). These overdoses have been associated with tachycardia, premature ventricular contractions, and myocardial ischemia (2). In our case, we speculate that the pulseless electrical activity probably represented ventricular tachycardia, which spontaneously converted to sinus rhythm. The short half-life of epinephrine may have been responsible for this favorable outcome. Physicians should be aware of the potential for adverse cardiovascular effects following voluntary intravenous injection with epinephrine.

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2. Karch SB. Coronary artery spasm induced by intravenous epinephrine overdose. Am J Emerg Med. 1989;7:485-8. [PMID: 2757714]
3. Merigian KS, Park LJ, Leeper KV, Browning RG, Giometi R. Adrenergic crisis from crack cocaine ingestion: report of five cases. J Emerg Med. 1994;12:485-90. [PMID: 7963395]

Correction: Multiple Measures of Adherence to HIV Protease Inhibitors

In an article on multiple measures of adherence to HIV protease inhibitors (1), subheadings in Table 2 were published incorrectly. Under the headings "Week 8" and "Week 24," the positions of the subheadings "Detectable Viral Load" and "Undetectable Viral Load" should be reversed.

Reference

1. Liu H, Golin CE, Miller LG, Hays RD, Beck CK, Sanandaji S, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med. 2001;134:968-77. [PMID: 11352698]

Correction: Guidelines for the Management of Patients with Chronic Stable Angina: Diagnosis and Risk Stratification

In a position paper about guidelines for chronic stable angina (1), the footnote to Table 5 and the third sentence of the fifth paragraph under the heading "Exercise Electrocardiography Testing" should read: "The Duke treadmill score equals the exercise time in minutes minus (five times the ST-segment deviation, during or after exercise, in millimeters) minus (0 if there is no angina, 4 if angina occurs, and 8 if angina is the reason for stopping the test)."

Reference

1. Williams SV, Fihn SD, Gibbons RJ. Guidelines for the management of patients with chronic stable angina: diagnosis and risk stratification. Ann Intern Med. 2001;135:530-47. [PMID: 11578158]

BOOK NOTES

Structured abstracts of information on newly published books, computer programs, selected Web sites, and other material are provided in this portion of Medical Writings. "Order phone" numbers can be used to place orders directly with publishers.

The Desktop Guide to Complementary and Alternative Medicine: An Evidence-Based Approach

Ernst E, ed. 444 pages. London: Harcourt Pub Ltd (Mosby); 2001. $34.95. ISBN 0723432074. Order phone 800-633-6699.

Field of medicine: Multidisciplinary.

Format: Paperback book includes a complete CD-ROM for rapid search capability and links to MEDLINE.

Audience: Primary care physicians and general internists.

Purpose: To summarize the available information on complementary and alternative medicine (CAM).

Content: The guide includes diagnostic methods, therapies, herbal and nonherbal medicines, and conditions for which CAM might be used. A general topics section with essays on the use of CAM in various countries and legal, ethical, safety, and economic issues is included. Ten diagnostic techniques unique to CAM are discussed, including bioresonance and kinesiology. The section on CAM therapies excludes medicines but includes such well-known techniques as acupuncture, biofeedback, and homeopathy. Multiple therapies without sufficient evidence of effectiveness are listed in tables. The medications section excludes vitamins and minerals in favor of herbals and nonherbal supplements. Tables list supplements without evidence of effectiveness and those with possible interactions with heart drugs, anticoagulants, antidiabetic drugs, and oral contraceptives. The section on conditions includes those seen in primary care for which CAM is popular. All the sections are extensively referenced to international published literature.

Highlights: Two features are particularly valuable: the broad scope of the various aspects of CAM covered and the extensive referencing and critical evaluations of the available literature. The listings of the conditions for which CAM is commonly used serve as an internal cross-index to the listings of the various therapies and medications.

Limitations: The list of useful Web sites for herbal medications does not include the Complete German Commission E Monographs, Therapeutic Guide to Herbal Medicines (http://home.mdconsult.com/about/book/IM.html), a compilation of 380 monographs with cross-references of each herb by ailment, body system, and interactions (also available in hardcover through the American Botanical Council). Many hard choices were made in an attempt to hold down both the size and price of this desktop guide.

Related reading: *Encyclopedia of Complementary Health Practice* (Springer, 1999) and the Health Reference Series *Alternative Medicine Sourcebook* (Omnigraphics, Inc., 1999) are popular references.

Reviewer: Roger P. Smith, PhD, Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, New Hampshire.

Infection Control Reference Service: The Experts' Guide to the Guidelines

Second edition. Abrutyn E, Goldmann DA, Scheckler WE, eds. 1578 pages. Philadelphia: WB Saunders; 2000. $329.00. ISBN 0721684688. Order phone 800-545-2522.

Field of medicine: Infection control.

Format: Hardcover book and searchable CD-ROM software. System requirements: Windows 95, 98, or NT; Pentium processor-based PC; 32 MB of available RAM; 10 MB of available hard-disk space; 8X or faster CD-ROM drive. Apple Power Macintosh or compatible computer: 32 MB of available RAM; 10 MB of available hard-disk space; 8X or faster CD-ROM drive.

Audience: Health care providers in inpatient, outpatient, home care, and long-term care settings.

Purpose: To gather and interpret infection control guidelines.

Content: The materials include 176 guidelines for infection control practices from diverse groups, including some from the Centers for Disease Control and Prevention (for example, "Recommendations for chemoprophylaxis after occupational exposure to HIV") and harder-to-find documents (such as "Hydrotherapy/Therapeutic Pool Infection Control Guidelines" from the American Physical Therapy Association). Commentary from infection control experts is also provided.

Usability: The book is highly usable; the CD-ROM doesn't add much, unfortunately.

Highlights: The compilation of all relevant guidelines in one location is a great service to infection control personnel. Nationally known authorities interpret the guidelines and fill in gaps. Many chapters include discussions of unresolved issues and suggestions for research. Contact information, including telephone numbers and Web addresses, is given for all organizations mentioned in the book.

Limitations: The accompanying CD-ROM version is searchable but is nothing more than the text from the book; no hypertext links are provided. On my copy, the index of the CD-ROM worked only through S; clicking on T through Z produced a blank screen. Clicking on "Online Resources" takes the reader to the publisher's Web site.

Related reading: Mayhall's *Hospital Epidemiology and Infection Control* (Lippincott Williams & Wilkins, 2000) covers the general principles of hospital epidemiology. The Society for Healthcare Epidemiology has compiled all of the Centers for Disease Control and Prevention guidelines in one volume and all of its position papers in another (www.SHEA-online.org). The National Guidelines Clearinghouse (www.guidelines.gov) is another valuable source of evidence-based guidelines.

Reviewer: Rebecca Wurtz, MD, MPH, Northwestern University, Chicago, Illinois.

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Switching from Prescription to Over the Counter

Under the federal laws governing the U.S. Food and Drug Administration (FDA) oversight of drugs, any drug that can safely be used by consumers without physician management should be available without a prescription. In 1951, the Durham–Humphrey Amendment to the Food, Drug, and Cosmetic Act established criteria for prescription and over-the-counter drugs. Habit-forming drugs listed in the statute are limited to prescription sale, as are drugs that must be administered, or their effects monitored, by a health professional.

Certain classes of drugs (e.g., toxic chemotherapy agents) are unlikely candidates for over-the-counter sale for obvious reasons. But drug makers, health insurers, and patient advocates are asking the FDA to consider allowing an increasingly wide variety of medications for over-the-counter sale. Their motives for seeking a switch vary almost as much as the drugs themselves, and the issues involved are growing more complex as the boundaries of the over-the-counter realm expand.

In 1972, the FDA began the ambitious task of evaluating all drug products sold over the counter. Seventeen expert panels reviewed 20 000 reports and other documents on the safety and efficacy of more than 700 ingredients (Clin Ther. 1991;13:200-15). The FDA then published a series of monographs that established standards for allowable ingredients and appropriate labeling for over-the-counter drugs. The panels also recommended 40 prescription drugs or dosage strengths for transfer to over-the-counter status.

Drugs may be changed from prescription to over-the-counter sale through several administrative mechanisms. Drugs can gain over-the-counter status if one of the FDA monographs describes their ingredients as safe and effective for a specified indication. Switches on many drugs—including analgesics, antihistamines, decongestants, sleep aids, antipruritics, and vaginal antifungal preparations—have used this mechanism over the past 2 decades. Second, the FDA evaluates requests to switch drugs to over-the-counter sale on a case-by-case basis, using a new-drug application (NDA) process similar to that used for new prescription drugs. A third approach, rarely used in the past, is to publish a new regulation that reclassifies a drug. Any interested party, including the FDA commissioner, may initiate this process. The FDA used this mechanism to switch the topical antifungal agent tolnaftate and the antitussive agent dextromethorphan.

For each NDA proposed, the FDA's Nonprescription Drugs Advisory Committee (NDAC) meets in joint session with the FDA advisory committee that has expertise on the category of drugs under consideration. The two committees evaluate the evidence for safety and efficacy and make a recommendation, which the FDA usually accepts.

The Nonprescription Drug Manufacturers Association estimates that more than 200 products that were once available only by prescription can now be purchased over the counter. The Consumer Healthcare Products Association reports that 80 ingredients, dosages, or indications have achieved over-the-counter status since 1976.

The rate of switching to over-the-counter status appears to be increasing. From the mid-1980s to the mid-1990s, approximately one drug was switched annually. A flurry of activity began in 1995, with the reclassification of several drug classes, including H_2-receptor antagonists for heartburn, nicotine gum and patches, pediatric analgesics, and hair-growth formulations.

OVER-THE-COUNTER DRUGS FOR CHRONIC CONDITIONS

Until now, the former prescription-only drugs granted over-the-counter approval were intended to treat acute or episodic conditions with recognizable symptoms—not chronic conditions or diseases requiring laboratory tests or signs on examination to make a diagnosis.

Use of over-the-counter drugs for chronic conditions is "the next big frontier," according to the Web site for Francesco International (www.rxtootc.com), a consulting company that specializes in over-the-counter switches and publishes a newsletter called *Switch*. An argument for expanding over-the-counter drug availability is that chronic health conditions are highly undertreated. This is because many Americans lack health insurance, many who have insurance seek medical care only for prominent symptoms, and even those who visit their physician may receive inadequate treatment for conditions with "silent" health risks—for example, hypertension or high cholesterol. If drugs to treat these conditions were available over the counter, the argument maintains, they might be more widely used.

That argument has serious caveats, however. For one, over-the-counter drugs are certain to be used by some people who will derive no benefit—and may even be harmed—because they do not really have the condition that the drug is designed to treat. This warning is particularly important with drugs that are meant to treat chronic conditions because the patient may take the drug for a long time, which may increase the chance of adverse effects. Even more sobering is the likelihood that people who need more aggressive disease management, including prescription drugs and close physician monitoring, will instead choose to use less effective over-the-counter drugs and avoid physician visits. Consumers may obtain a false sense of security at great cost to their health. Besides individual safety, public health concerns, such as the risk for antimicrobial resistance, may come into play. Decisions about over-the-counter availability involve weighing these pros and cons, and the FDA commonly requires drug makers to conduct additional studies to demonstrate that switching to over-the-counter availability will yield a net benefit.

In a recent article on switching drugs from prescription to over-the-counter sales, Eric Brass, MD, PhD, chair of the Department of Medicine, Division of Clinical Pharmacology at the Harbor–UCLA Medical Center in Torrance, California, wrote that "The dangers of misdiagnosis involve both the potential adverse effects of the drug when inappropriately used and the risks associated with lack of treatment for the actual cause of the symptoms" (N Engl J Med. 2001;345:810-6).

However, economics—not safety or public health—typically sets the process for an over-the-counter switch in motion. Naturally, drug manufacturers will ask for a switch only if the move increases their profits. Many drugs make the switch to over-the-counter availability because of a "generic defense," said Steve Francesco, president of Francesco International. When a drug patent is about to expire, the company submits a switch request in the hopes that brand recognition and loyalty cultivated among prescription customers will transfer to the over-the-counter market. The Waxman–Hatch Act of 1984 added another incentive: granting 3 additional years of market exclusivity to drug makers if they perform the extra clinical trials required to gain over-the-counter approval.

If a drug has proved to be safe and effective when dispensed on a prescription-only basis and the over-the-counter request is for the same indication at the same or a lower dose, the FDA focuses on evidence that patients can use the drug properly without physician guidance. This evidence often comes from "actual-use" studies, which attempt to mimic consumer use of over-the-counter drugs, and label-comprehension studies, to see how well consumers can extract critical information from package labels.

"The studies performed to switch a drug often test the consumer more than they test the drug," wrote Randy P. Juhl, PhD, RPh, dean of the University of Pittsburgh School of Pharmacy in Pennsylvania (Clin Ther. 1998;20 Suppl C:C111-7). He notes that the studies must address four questions: "Can they read the label? Can they understand the label? Do they follow the label? And do they achieve the desired outcome? All four levels of inquiry help to determine whether a consumer can use a product [safely and effectively]."

Brass noted that actual-use studies are difficult to conduct because little is known about how to simulate consumer behavior in the real world. One common approach is a mall-intercept study, in which prospective participants are solicited and screened at shopping mall booths.

Prilosec—the world's best-selling drug (sold as Losec outside the United States), with 2000 sales of $6.2 billion—illustrates many aspects of the over-the-counter switching process. Prilosec (omeprazole) is a proton-pump inhibitor used to treat gastroesophageal reflux disease. The expiration of the basic patent for Prilosec, held by AstraZeneca PLC (London, United Kingdom), expired in October 2001, and this appears to open the market to generic competition. The company has taken several steps to protect its market share. It has filed lawsuits claiming that several additional patents for omeprazole should extend its rights to exclusive marketing of the drug through 2007. In addition, AstraZeneca has introduced a second-generation proton-pump inhibitor, Nexium (esomeprazole). The company also sought FDA approval for over-the-counter marketing of Prilosec in 10-mg pills, half the prescription dose. AstraZeneca already negotiated with The Procter & Gamble Co. (Cincinnati, Ohio) to sell an over-the-counter version of Prilosec in the United States. However, at an October 2000 meeting, the NDAC voted against the switch, citing the need for more data on the drug's long-term effects and evidence that consumers understand how and when to appropriately use the over-the-counter version. The committee expressed concern that as a result of easy access to Prilosec, people with serious gastric conditions might not seek medical attention.

SWITCH PETITION BY INSURER OPPOSED BY DRUG MAKERS

Until recently, a petition from an "interested third party" had never been used to begin the process of reclassifying a drug, although this is a legal option. However, in July 1998, WellPoint Health Networks, the parent company of Blue Cross of California, submitted a citizen's petition asking the FDA to switch the nonsedating antihistamines Allegra, Claritin, and Zyrtec to over-the-counter status for treatment of allergic rhinitis. The insurer offered evidence that these drugs are at least as safe and effective as older antihistamines that are already sold over the counter. However, another issue was at stake for Blue Cross: Over-the-counter status would allow the company to stop covering these drugs as a prescription-drug benefit. Patients, not the insurer, would pay for these drugs, resulting in substantial cost saving for the insurer.

The FDA considers only safety and efficacy—not economic issues, said Linda Katz, MD, MPH, deputy director of the FDA's Division of Over-the-Counter Drug Products. In May 2001, the NDAC and the Pulmonary–Allergy Drugs Advisory Committee voted by a wide margin to allow over-the-counter sale of the antihistamines. Alastair J.J. Wood, MD, an NDAC member and assistant vice chancellor for research at Vanderbilt University in Nashville, Tennessee, said that there was a clear answer to the question of whether patients could be expected to appropriately diagnose allergic rhinitis themselves: "The answer was yes, if for no other reason than there were already sedating antihistamines on the market for treatment of allergic rhinitis." Thus, many of these same companies had already fought that battle when they previously sought approval for over-the-counter sale of older antihistamines.

However, this time the drug manufacturers opposed the switch to over-the-counter status for nonsedating antihistamines. A switch would probably mean lower prices for the drug. The drug makers argue that patients might incorrectly diagnose and use the drugs to treat asthma or other conditions. Schering-Plough, which manufactures Claritin, maintained that the switch "would force patients to self-diagnose, self-treat, and pay the entire cost of their allergy medications, thus raising serious questions about quality of care and costs for patients." The company added, "A switch over a sponsor's objections would constitute an unprecedented departure from past agency policy and implicate the sponsor's statutory and constitutional rights." The American Academy of Allergy, Asthma, and Immunology, which represents 6000 physicians, also opposed the switch.

The case remains under review by the FDA. Dr. Katz pointed to the Code of Federal Regulations, which states (21CFR310.200), "A proposal to exempt a drug from the prescription-dispensing requirements . . . may be initiated by the Commissioner or by any interested person. Any interested person may file a petition seeking such exemption. The petition may be pursuant to [the code section outlining procedures for a citizen's petition], or in the form of a supplement to an approved new drug application." The FDA commissioner may approve, deny, or provide a tentative response to citizens' petitions.

In June 2000, the FDA held 2 days of public hearings on over-the-counter drug availability. At the hearings, Allan Korn, MD, senior vice president and chief medical officer of the Blue Cross and Blue Shield Association, said that the FDA should take a more active role in over-the-counter switches by initiating its own review of the evidence. He urged the agency to adopt "a structured process for switching drugs from prescription to over-the-counter status" and suggested starting with a review of over-the-counter drugs in other industrialized nations.

"This review should not be a one-time effort, but we believe an ongoing and continuous activity within the FDA," Korn added. "Another basis for review should be individually initiated petitions that are supported by credible information meeting switch criteria. Many parties, other than manufacturers, have an interest in the switch process . . . We do not believe that the designation of a drug should be purely an economic decision made by the manufacturer of the drug, perhaps for its own self-interest."

Not surprisingly, the pharmaceutical industry opposes any move that would take switch decisions out of its hands. Russel A. Bantham, JD, executive vice president and general counsel of the Pharmaceutical Research and Manufacturers of America, testified at the FDA hearing: "Manufacturers are in the best position to decide when to begin the switch process and thereby avoid premature switches that could put some members of the public at risk . . . It is not within FDA's authority to force a manufacturer fundamentally to change the conditions of use of its product from prescription to nonprescription status."

THREE OTHER DEBATES

Emergency Contraception

Another major topic of the June 2000 hearings was whether to sell emergency contraceptives over the counter. Women's-health advocates said that the move is overdue. The drug is available without prescription in the United Kingdom and Canada, and several U.S. states have physician–pharmacist agreements allowing women to purchase these pills without seeing a physician.

Opponents argue that over-the-counter emergency contraception could discourage use of conventional birth control methods. However, a study at the University of Edinburgh, Scotland, found otherwise. In this study, half the women received emergency contraceptive pills to take home and half had to visit their physician to obtain them (N Engl J Med. 1998;339:1-4). The take-home group used emergency contraception more frequently than the control group but also used conventional contraceptive methods at the same rate as the control group.

Frank Davidoff, MD, a clinical professor at the University of Connecticut Medical School, Farmington, Connecticut, and an *Annals* editor emeritus, noted that unusual convergences of interests sometimes emerge when over-the-counter decisions are debated. For example, religious groups and other staunch opponents of birth control may find allies in physician organizations. The practitioners who prescribe the drugs—obstetricians and gynecologists, in the case of birth control—may see their office practice threatened, because if people can go to the drugstore and get what they need, or what they think they need, they don't have to visit a physician. "When they (physicians) testify before the FDA, they find all sorts of reasons the drug should remain on prescription, but the skeptics' perception is that they just don't want to lose their business," Davidoff noted.

Antimicrobials

For antimicrobial drugs, issues of individual safety may take a back seat to public health. In a move that surprised industry insiders, the FDA in December 1998 denied a switch request, largely because of fears of antiviral resistance, for the antiherpes drug penciclovir (Denavir), now marketed by Novartis (East Hanover, New Jersey). Observers had predicted that as a topical preparation against cold sores, penciclovir would face easy over-the-counter approval. However, according to Brass, "The issue of resistance just dominated those [advisory committee] discussions." The Infectious Disease Drug Committee indicated that, regardless of the data presented, it would not support the over-the-counter availability of antimicrobials because of the serious threat of antibiotic resistance. Katz of the FDA said that because antiviral drugs are similar to one another, their indiscriminate use could lead to the emergence of cross-resistance against other antivirals, including those used for neonatal herpes.

Statins

The statins used to lower cholesterol levels are another drug class for which manufacturers are seeking over-the-counter approval. In 1997, the FDA issued a guideline stating that lowering of cholesterol levels is not an appropriate indication for over-the-counter approval because physician monitoring is required. The drug makers pursued over-the-counter status anyway, targeting people whose cholesterol levels are higher than optimal but not high enough to meet physicians' criteria for drug treatment.

The issue is a tricky one. Although studies suggest that many people who could benefit from statins are not using them, no information is available on how well patients would do at diagnosing and treating hypercholesterolemia on their own.

"You know when you need contraception or when you need an antihistamine," Wood said, "but you may not know when you need [to lower] cholesterol [levels] . . . and you certainly may not know whether it's been effective or not."

Brass stated that for high cholesterol levels, as for many chronic conditions, "If optimal care requires regular attention by a health care provider—even if it's not for the drug itself but for the overall integrative treatment—it becomes harder to envision the role of over-the-counter availability."

The early rounds of over-the-counter switches were relatively straightforward, focusing on acute-indication drugs, Brass noted. However, he predicted, "The next round of products may raise some different issues, and we're still on the learning curve with respect to those."

—*Tom Reynolds*

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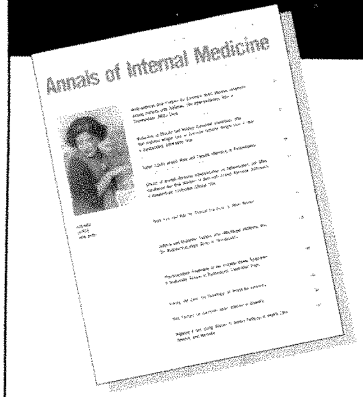

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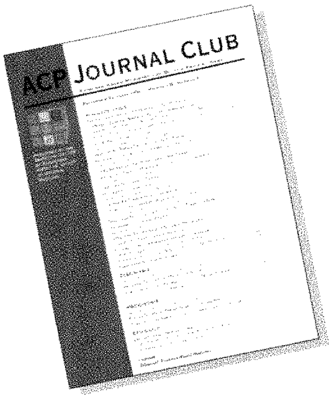

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The patient is 175 cm (69 in) tall and weighs 50 kg (110 lb). Blood pressure is 115/70 mm Hg, pulse is 96/min, and temperature is 36.9 °C (98.4 °F). The skin shows a truncal and proximal extremity rash consisting of grouped vesicles on an erythematous base. There is also evidence of excoriation. The remainder of the physical examination, including pelvic and rectal examination, is otherwise normal, and stool is negative for occult blood. The neurologic examination is normal.

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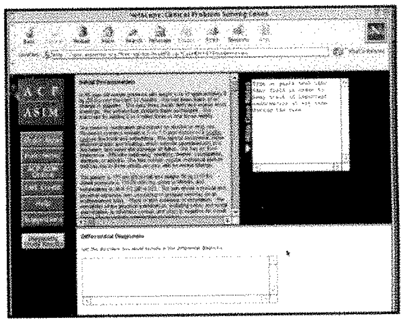

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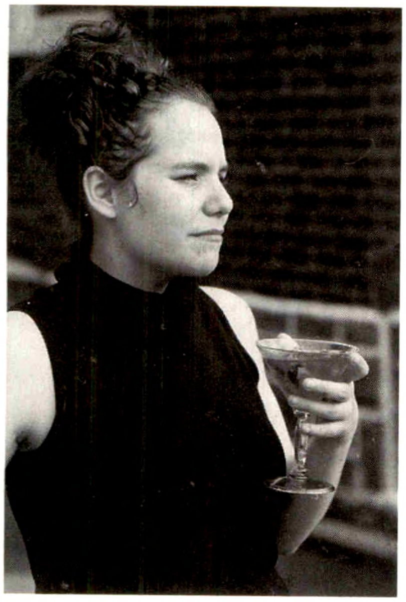

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ACP
ASIM

UR PATIENT:
A 45-year-old woman
esents with weight loss of
proximately 9 kg (20 lb)
er the past 12 months. She
s been aware of no change
appetite. She eats three
eals daily and snacks most
enings. Her activity has
nilarly been unchanged.
e exercises by walking 2 to
niles three or four times
ekly. She takes no medica-
n and reports no alcohol or
ıg use. Review of systems
veals a 1- to 1.5-year history
a pruritic rash on the trunk
d extremities. She reports
casional vague abdominal
in and bloating, which sub-
e spontaneously in a few
urs, and notes the passage
flatus. She has no food
olerance, difficulty swal-
ving, sweating, tremor, con-
pation, diarrhea, or arthri-
She has normal, regular
nstrual periods and has
o to three stools per day,
th no recent change.
The patient is 175 cm (69
tall and weighs 50 kg (110
Blood pressure is 115/70
n Hg, pulse is 96/min, and
nperature is 36.9 °C (98.4
. The skin shows a truncal
d proximal extremity rash
nsisting of grouped vesicles
an erythematous base.
ere is also evidence of
coriation. The remainder of
physical examination,
luding pelvic and rectal
amination, is otherwise
rmal, and stool is negative
occult blood. The neuro-
ic examination is normal.

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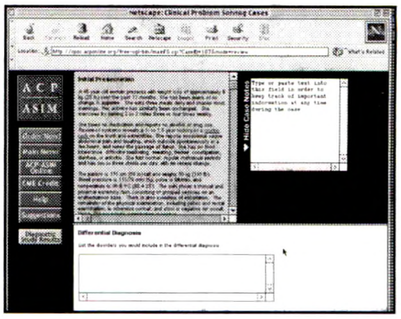

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C.R. Walsh, M.G. Larson, J.C. Evans, L. Djousse, R.C. Ellison, R.S. Vasan, and D. Levy

In the community, alcohol consumption is not associated with increased risk for congestive heart failure, even among heavy drinkers (≥15 drinks/wk in men and ≥8 drinks/wk in women). To the contrary, when consumed in moderation, alcohol appears to protect against congestive heart failure.

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J.M. Nicolás, J. Fernández-Solà, R. Estruch, J.C. Paré, E. Sacanella, A. Urbano-Márquez, and E. Rubin

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W.C. Meeker and S. Haldeman

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Evaluation and Management of HIV-Infected Women 228

A.M. Levine

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Medical Professionalism in the New Millennium: A Physician Charter 243

Project of the ABIM Foundation, ACP–ASIM Foundation, and European Federation of Internal Medicine

To maintain the fidelity of medicine's social contract during this turbulent time, we believe that physicians must reaffirm their active dedication to the principles of professionalism, which entails not only their personal commitment to the welfare of their patients but also collective efforts to improve the health care system for the welfare of society. This Charter on Medical Professionalism is intended to encourage such dedication.

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Stirred, Not Shaken 247

J. Wynne

Given the widespread use of alcoholic beverages in the western world, let us hope that the provocative studies by Walsh and Nicolás and their colleagues reported in this issue will stir researchers to gain further understanding of the cardiovascular effects of alcohol.

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ON BEING A DOCTOR

Emergency 250

R.A. Carson

As I cross through the trauma center garage where I park my car, on the ground floor beneath the helipad, a man approaches me, disheveled, emaciated, his eyes a little wild. I try to seem nonchalant, but I'm no longer preoccupied with anything but my immediate surroundings. I'm focused. The man has my attention.

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The Landscape and Lexicon of Blinding in Randomized Trials 254

K.F. Schulz, I. Chalmers, and D.G. Altman

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The Appendix for the Information for Authors is published in the first issues of January and July. Please refer to the Appendix for information on manuscript format, style (manuscript typing and assembly), headings in text, style guidelines, title page, abstract, methods and results, discussion and conclusions, references, footnotes, tables and figures, acknowledgments, and current mailing address), and publication (scheduling of papers and proofs, ordering reprints, and complimentary copies).

Annals of Internal Medicine | ARTICLE

Alcohol Consumption and Risk for Congestive Heart Failure in the Framingham Heart Study

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Background: Although excessive alcohol consumption can promote cardiomyopathy, little is known about the association between alcohol consumption and risk for congestive heart failure in the community.

Objective: To determine the relation between alcohol consumption and risk for congestive heart failure in the community.

Design: Community-based, prospective observational study.

Setting: Framingham, Massachusetts.

Participants: Participants in the Framingham Heart Study who were free of congestive heart failure and coronary heart disease.

Measurements: Self-reported alcohol consumption; sex-specific rates of congestive heart failure per 1000 person-years of follow-up by level of alcohol consumption.

Results: In men, 99 cases of congestive heart failure occurred during 26 035 person-years of follow-up. In women, 120 cases of congestive heart failure occurred during 35 563 person-years of follow-up. After adjustment for multiple confounders, risk for congestive heart failure was lower among men at all levels of alcohol consumption compared with men who consumed less than 1 drink/wk. The hazard ratio for congestive heart failure was lowest among men who consumed 8 to 14 drinks/wk (0.41 [95% CI, 0.21 to 0.81]) compared with those who consumed less than 1 drink/wk. In women, the age-adjusted hazard ratio for congestive heart failure was lowest among those who consumed 3 to 7 drinks/wk (0.49 [CI, 0.25 to 0.96]) compared with those who consumed less than 1 drink/wk. However, after adjustment for multiple predictors of congestive heart failure, this association was no longer statistically significant.

Conclusions: In the community, alcohol consumption is not associated with increased risk for congestive heart failure, even among heavy drinkers (≥15 drinks/wk in men and ≥8 drinks/wk in women). To the contrary, when consumed in moderation, alcohol appears to protect against congestive heart failure.

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See related article on pp 192-200 and editorial comment on pp 247-249.

Regular, heavy consumption of alcohol is associated with subclinical impairment of left ventricular function (1–3) and occasionally results in overt cardiomyopathy (4). This may be a consequence of direct toxic effects of alcohol or its metabolites (5); coexisting malnutrition (6); associated hypertension (7, 8); increased ventricular mass (9) or, rarely, toxic additives to alcoholic beverages (10). Conversely, moderate alcohol consumption appears to be protective against coronary heart disease (11–14). Myocardial infarction is an important risk factor for congestive heart failure (15–18). By preventing coronary heart disease, moderate alcohol consumption may indirectly protect against congestive heart failure secondary to myocardial infarction. Thus, the relation of alcohol consumption to the risk for congestive heart failure is probably complex, reflecting the interplay of its coronary protective effects and its myocardial toxic effects.

Little is known about the effect of alcohol consumption on the incidence of congestive heart failure in community-based populations. We therefore sought to determine the relation between alcohol consumption and risk for congestive heart failure in participants in the Framingham Heart Study.

METHODS

Study Sample

The Framingham Heart Study is a prospective epidemiologic cohort study established in 1948 to evaluate potential risk factors for coronary heart disease. The original cohort consisted of 5209 residents of Framingham, Massachusetts, 28 to 62 years of age at entry, who have undergone follow-up evaluations every 2 years. In 1971, 5124 additional participants (the offspring of the original participants and their spouses) were enrolled into the Framingham Offspring Study. These participants undergo follow-up evaluations every 4 years. The study design and entry criteria for both cohorts are described elsewhere (19–22).

The study sample was drawn from members of the original cohort who attended examination 12, 15, 17, 20, or 22 (1971 to 1994) and members of the offspring cohort who attended examination 2, 4, or 5 (1979 to 1995). Each of these examinations served as the baseline for subsequent follow-up intervals. Participants with complete information on alcohol consumption at a baseline examination and an examination 6 to 10 years earlier (to identify former drinkers) were eligible for the analysis. All examinations and procedures were approved by the institutional review board of Boston University School of Medicine, and all participants gave informed consent.

Ascertainment of Alcohol Consumption

At examinations 12 through 15 and 17 through 22 of the original cohort and at all examinations of the offspring cohort, participants were asked about the number of 1.5-oz cocktails, 12-oz glasses (or cans) of beer, and 4-oz glasses of wine they consumed in 1 week. Alcohol intake (g/wk) among participants who consumed at least 1 drink/wk was computed by using the following equation: 28.35 + (0.57 + the number of cocktails per week + 0.44 + the number of beers per week + 0.40 + the number of glasses of wine per week) (23). For each participant, the number of drinks consumed per week was calculated by assuming that each drink contains 13 g of alcohol (24). Men who consumed 15 drinks/wk or more and women who consumed 8 drinks/wk or more were considered to be heavy drinkers in accordance with definitions established by the National Institute of Alcohol Abuse and Alcoholism (25).

Participants who reported consuming less than 1 drink/wk at the index examination were further separated into two groups on the basis of reported alcohol consumption at an examination 6 to 10 years before the index examination. Participants who reported consumption of less than 1 drink/wk at the index examination but more than 1 drink/wk at the previous examination were classified as former drinkers. Participants who reported consumption of less than 1 drink/wk at both examinations were classified as nondrinkers and served as the reference group.

Baseline Measurements

Medical histories and physical examinations were performed for each participant at every clinic visit. Systolic and diastolic blood pressure were measured twice in the left arm of each participant. The average of the two readings was used for each blood pressure variable. The diagnosis of hypertension was based on a systolic blood pressure of 140 mm Hg or greater, a diastolic blood pressure of 90 mm Hg or greater, or current use of antihypertensive drugs (26). Total and high-density lipoprotein (HDL) cholesterol levels were measured at each examination except examination 17 of the original cohort. For participants attending examination 17, total and HDL cholesterol levels measured at examination 15 were used. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Participants were separated according to smoking status into nonsmokers, former smokers, and current smokers (those who smoked cigarettes regularly within 1 year of the index examination). The number of cigarettes smoked per day was recorded for current smokers. Diabetes was defined as a nonfasting blood glucose level of 11.1 mmol/L or greater (≥200 mg/dL), a fasting blood glucose level of 7.8 mmol/L or greater (≥140 mg/dL), or use of insulin or an oral hypoglycemic agent (27). Diagnostic criteria for coronary heart disease (including myocardial infarction, coronary insufficiency, and angina pectoris) are described elsewhere (22). Valvular heart disease was defined as the presence of a systolic murmur louder than II/VI or any diastolic murmur. Electrocardiographic left ventricular hypertrophy was diagnosed if a participant had voltage criteria for left ventricular hypertrophy accompanied by lateral repolarization changes (28).

Outcome Measurements

The primary outcome of interest was incident congestive heart failure. Participants were monitored for the development of congestive heart failure and other cardiovascular events by using routine periodic clinic examinations and surveillance procedures. Information about such events was obtained through medical history, physical examination, and hospitalization records and by communication with personal physicians. All suspected new events were reviewed by a panel of three experienced investigators who evaluated all pertinent medical and hospital records and pathology reports. **Table 1** shows criteria for diagnosis of congestive heart failure. Congestive heart failure was diagnosed if at least two major criteria or one major and two minor criteria were present. Minor criteria were acceptable only if they could not be attributed to another medical condition (such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome) (29).

The criteria used to identify participants with congestive heart failure in the Framingham Heart Study compare favorably to other clinically based criteria used to identify persons with congestive heart failure (30) and left ventricular systolic dysfunction (31). Mosterd and colleagues (30) reported that the Framingham Heart Study criteria were 100% sensitive and 78% specific for identifying persons with definite congestive heart failure as determined by clinical assessment by a cardiologist.

Statistical Analysis

Separate analyses were performed for men and women. Because men and women differed markedly in reported alcohol intake, level of alcohol consumption was categorized differently for each sex. Baseline risk factors were computed for each level of alcohol consumption. Age-adjusted and multivariable-adjusted hazard ratios for congestive heart failure were calculated by using Cox proportional hazards regression models (32), with pooled follow-up periods and reported alcohol intake at original cohort examinations 12, 15, 17, 20, and 22 and offspring cohort examinations 2, 4, and 5. Nondrinkers served as the reference group. The following covariates were included in the multivariable-adjusted models: age, smoking (cigarettes/d), body mass index, diabetes, valvular heart disease, HDL cholesterol level, and hypertension. The maximum duration of follow-up was 5 years. For participants attending consecutive examinations that were fewer than 5 years apart (original cohort examinations 15 and 17, and 20 and 22 and offspring examinations 4 and 5), follow-up was censored at the time of the repeated examination (approximately 4 years later). Participants who attended more than one index examination could contribute to multiple observations periods. We used the Anderson–Gill model for multiple failure times (33) to account for the potential for clustering of observations by participant.

Because the effect of alcohol consumption on development of congestive heart failure may be mediated through the effects of alcohol on hypertension or HDL cholesterol level, we performed secondary analyses using multivariable-adjusted models, with and without hypertension status and HDL cholesterol as covariates. To determine the association between alcohol consumption and risk for congestive heart failure without interceding myocardial infarction, we calculated age-adjusted and multivariable-adjusted hazard ratios, censoring participants at the time of myocardial infarction that occurred during follow-up. To adjust for differences in medical therapy across alcohol consumption categories, models were constructed that adjusted for medications taken at the index examination (aspirin, β-blockers, diuretics, calcium-channel blockers, and angiotensin-converting enzyme inhibitors) in addition to the covariates included in the model used for the primary analysis. For the final model, the proportional hazards assumption was tested and found to be appropriate. Analyses for length-selection biases showed that from the earliest ascertainment of alcohol consumption in the Framingham Study until the period of the current primary analysis, heavy drinkers were not at increased risk for congestive heart failure or death compared with nondrinkers. All statistical analyses were performed by using SAS statistical software (34).

Table 1. **Criteria for Congestive Heart Failure***

Major criteria
Paroxysmal nocturnal dyspnea
Neck-vein distention
Rales
Radiographic cardiomegaly (increasing heart size on chest radiography)
Acute pulmonary edema
S_3 gallop
Increased central venous pressure (>16 cm H_2O at right atrium)
Hepatojugular reflux
Pulmonary edema, visceral congestion, or cardiomegaly at autopsy
Minor criteria
Bilateral ankle edema
Nocturnal cough
Dyspnea on ordinary exertion
Hepatomegaly
Pleural effusion
Decrease in vital capacity by one third from maximum recorded
Tachycardia (heart rate ≥ 120 beats/min)

* Congestive heart failure was diagnosed if at least two major criteria or one major and two minor criteria were met.

RESULTS

Participants

A total of 3498 men and 4188 women attended at least one baseline examination. We excluded 131 men and 217 women because of missing information on covariates or failure to attend a follow-up examination. An additional 218 men and 245 women were excluded because of missing information on alcohol consumption,

Table 2. **Baseline Characteristics in Men, by Level of Alcohol Consumption***

Characteristic	Alcohol Consumption				
	Nondrinkers	Former Drinkers	1–7 Drinks/wk	8–14 Drinks/wk	≥15 Drinks/wk
Age, *y*	62.7 ± 11.7	60.8 ± 11.7	59.1 ± 11.3	59.6 ± 11.3	58.7 ± 10.7
Body mass index, *kg/m²*	27.2 ± 4.3	27.3 ± 4.1	27.3 ± 3.7	27.2 ± 3.6	27.2 ± 3.7
Hypertension, %	50.7	48.6	42.8	47.4	51.8
Medications, %					
Aspirin	36.7	26.4	43.1	38.3	42.2
Diuretics	12.6	15.6	11.9	12.7	15.0
β-Blockers	9.0	8.6	7.2	8.1	9.0
Calcium-channel blockers	6.6	6.4	4.4	3.3	3.3
Angiotensin-converting enzyme inhibitors	10.2	7.7	7.2	8.2	9.1
Total cholesterol level, *mmol/L (mg/dL)*	5.2 ± 1.0 (202.8 ± 38.2)	5.4 ± 1.0 (208.2 ± 37.9)	5.4 ± 1.0 (210.0 ± 37.3)	5.5 ± 0.9 (211.6 ± 35.7)	5.5 ± 0.9 (214.2 ± 36.3)
HDL cholesterol level, *mmol/L (mg/dL)*	1.0 ± 0.3 (39.5 ± 10.2)	1.0 ± 0.3 (40.4 ± 10.8)	1.1 ± 0.3 (42.3 ± 10.9)	1.2 ± 0.3 (46.4 ± 12.2)	1.3 ± 0.4 (48.8 ± 13.9)
Diabetes, %	8.6	10.0	7.1	5.6	6.4
Valvular heart disease, %	5.6	4.3	4.4	4.8	4.3
Smoking status, %					
Never	33.1	26.8	29.5	21.8	16.0
Former	47.4	51.1	52.0	54.6	53.0
Current	19.5	22.1	18.5	23.6	31.0
Cigarettes smoked daily, *n*†	23.8 ± 14.4	25.3 ± 13.8	22.4 ± 11.7	22.2 ± 12.9	26.2 ± 14.2
Alcohol intake, *drinks/wk*	0	0	3.6 ± 2.1	11.1 ± 2.3	27.3 ± 16.2
Previous alcohol intake, *drinks/wk*‡	0	8.9 ± 16.1	6.4 ± 7.8	12.5 ± 9.2	23.4 ± 17.6

* Data with the plus/minus sign are the mean ± SD. HDL = high-density lipoprotein.
† Current smokers only.
‡ Reported alcohol consumption at an examination 6 to 10 years before the index examination.

and 353 men and 233 women were excluded because of congestive heart failure or coronary heart disease at baseline, leaving 2796 men and 3493 women for analysis. Tables 2 and 3 show baseline characteristics of men and women, respectively.

Alcohol Consumption and Risk for Congestive Heart Failure

In men, 99 cases of congestive heart failure occurred during 26 035 person-years of follow-up. In women, 120 cases of congestive heart failure occurred during 35 563 person-years of follow up. Table 4 shows the age-adjusted incidence of congestive heart failure in men and women, by level of alcohol consumption.

Among men, risk for congestive heart failure was lower at all levels of alcohol consumption compared with nondrinkers after adjustment for age, smoking, body mass index, diabetes, valvular heart disease, and hypertension (Table 5). The hazard ratio for congestive heart failure was lowest among men who consumed 8 to 14 drinks/wk. Among women, the age-adjusted risk for congestive heart failure was reduced among those who consumed 3 to 7 drinks/wk compared with nondrinkers (Table 6), but after further adjustment for smoking, body mass index, diabetes, valvular heart disease, and hypertension, the association was only marginally statistically significant ($P = 0.05$). Further adjustment for medications used at the index examination (aspirin, β-blockers, diuretics, angiotensin-converting enzyme inhibitors, and calcium-channel blockers) did not materially change the results of the proportional hazards models (data available from the authors on request).

In secondary analysis, removal of hypertension from the proportional hazards models did not greatly change the observed hazard ratios in both men and women (data not shown). In men, addition of HDL cholesterol to the multivariable-adjusted model attenuated the association between alcohol consumption and risk for congestive heart failure. However, risk for congestive heart failure remained significantly lower in men who consumed 1 to 7 drinks/wk ($P < 0.01$) or 8 to 14 drinks/wk ($P = 0.03$) compared with nondrinkers (Table 5). Risk for congestive heart failure did not significantly differ in former drinkers compared with nondrinkers among men ($P = 0.2$) or women ($P > 0.2$).

Table 3. **Baseline Characteristics in Women, by Level of Alcohol Consumption***

Characteristic	Alcohol Consumption				
	Nondrinkers	Former Drinkers	1–2 Drinks/wk	3–7 Drinks/wk	≥8 Drinks/wk
Age, *y*	65.8 ± 12.4	63.4 ± 12.3	60.2 ± 11.2	59.9 ± 11.6	60.1 ± 10.9
Body mass index, kg/m^2	26.9 ± 5.5	26.5 ± 5.0	26.3 ± 4.9	25.6 ± 4.6	24.9 ± 4.3
Hypertension, %	54.9	49.2	44.2	40.8	47.8
Medications, %					
Aspirin	34.2	27.0	43.3	38.7	43.1
Diuretics	24.8	24.4	19.6	16.6	20.4
β-Blockers	8.7	7.3	6.7	6.4	7.1
Calcium-channel blockers	5.7	3.1	4.2	2.4	4.5
Angiotensin-converting enzyme inhibitors	7.5	5.9	5.1	5.8	6.1
Total cholesterol level, *mmol/L (mg/dL)*	5.8 ± 1.1 (223.3 ± 42.9)	5.8 ± 1.1 (225.5 ± 41.5)	5.7 ± 1.1 (221.7 ± 42.1)	5.7 ± 1.0 (220.0 ± 40.2)	5.8 ± 1.1 (226.0 ± 42.5)
HDL cholesterol level, *mmol/L (mg/dL)*	1.3 ± 0.3 (51.3 ± 13.5)	1.4 ± 0.4 (53.2 ± 15.0)	1.4 ± 0.4 (54.6 ± 14.2)	1.5 ± 0.4 (57.9 ± 15.4)	1.6 ± 0.4 (62.5 ± 16.9)
Diabetes, %	9.6	7.4	6.0	7.6	6.6
Valvular heart disease, %	8.1	6.2	4.8	4.7	6.0
Smoking status, %					
Never	60.3	46.1	45.1	36.8	21.6
Former	23.8	33.2	35.2	39.8	41.4
Current	15.9	20.7	19.7	23.4	37.0
Cigarettes smoked daily, *n*†	19.4 ± 10.5	17.9 ± 11.1	17.6 ± 10.7	18.0 ± 11.3	19.8 ± 11.3
Alcohol intake, *drinks/wk*	0	0	1.4 ± 0.5	4.9 ± 1.6	14.5 ± 6.8
Previous alcohol intake, *drinks/wk*‡	0	3.3 ± 5.3	2.5 ± 3.4	6.0 ± 11.5	11.4 ± 8.2

* Data with the plus/minus sign are the mean ± SD. HDL = high-density lipoprotein.
† Current smokers only.
‡ Reported alcohol consumption at an examination 6 to 10 years before the index examination.

Heavy Alcohol Consumption and Risk for Congestive Heart Failure

In our sample, 23% of men consumed 15 drinks/wk or more and 17% of women consumed 8 drinks/wk or more. The risk for congestive heart failure in men who consumed 15 drinks/wk or more was lower compared with nondrinkers after adjustment for age, smoking, body mass index, diabetes, valvular heart disease, and hypertension (Table 5). Risk for congestive heart failure among women who consumed 8 drinks/wk or more was not increased compared with nondrinkers (Table 6).

Table 4. **Age-Adjusted Incidence of Congestive Heart Failure in Men and Women, by Level of Alcohol Consumption**

Participants	All-Cause Congestive Heart Failure			Congestive Heart Failure without Preceding Myocardial Infarction		
	Cases	Follow-up	Age-Adjusted Incidence (95% CI)	Cases	Follow-up	Age-Adjusted Incidence (95% CI)
	n	*person-years*	*cases/1000 person-years*	*n*	*person-years*	*cases/1000 person-years*
Men						
Nondrinkers	24	2921	6.3 (3.7–8.8)	17	2869	4.7 (2.4–6.9)
Former drinkers	16	3254	4.5 (2.3–6.7)	10	3222	2.9 (1.1–4.7)
1–7 drinks/wk	27	9431	3.0 (1.9–4.1)	18	9341	2.0 (1.0–3.0)
8–14 drinks/wk	13	4450	2.9 (1.3–4.6)	11	4428	2.5 (1.0–4.0)
≥15 drinks/wk	19	5979	3.6 (1.9–5.2)	15	5942	2.9 (1.4–4.4)
Women						
Nondrinkers	44	7733	4.1 (2.8–5.4)	30	7711	2.9 (1.8–4.0)
Former drinkers	29	6181	4.1 (2.6–5.6)	16	6151	2.3 (1.1–3.4)
1–2 drinks/wk	21	8753	2.7 (1.5–3.9)	20	8723	2.6 (1.4–3.7)
3–7 drinks/wk	11	6829	1.9 (0.8–3.1)	8	6815	1.4 (0.4–2.4)
≥8 drinks/wk	15	6067	3.4 (1.6–5.2)	11	6056	2.3 (0.8–3.7)

Table 5. **Risk for Congestive Heart Failure in Men, by Level of Alcohol Consumption**

Disease	Hazard Ratio (95% CI)				
	Nondrinkers	Former Drinkers	1–7 Drinks/wk	8–14 Drinks/wk	≥15 Drinks/wk
All-cause congestive heart failure					
Age-adjusted model	1.0 (referent)	0.72 (0.38–1.37)	0.48 (0.27–0.83)	0.47 (0.24–0.93)	0.59 (0.32–1.08)
Multivariable-adjusted model 1*	1.0 (referent)	0.63 (0.33–1.20)	0.44 (0.25–0.77)	0.41 (0.21–0.81)	0.53 (0.29–0.97)
Multivariable-adjusted model 2†	1.0 (referent)	0.64 (0.34–1.22)	0.46 (0.27–0.81)	0.47 (0.24–0.94)	0.63 (0.34–1.19)
Congestive heart failure without preceding myocardial infarction					
Age-adjusted model	1.0 (referent)	0.65 (0.30–1.43)	0.45 (0.23–0.89)	0.57 (0.27–1.23)	0.66 (0.33–1.33)
Multivariable-adjusted model 1*	1.0 (referent)	0.54 (0.25–1.20)	0.41 (0.21–0.79)	0.49 (0.23–1.05)	0.59 (0.29–1.20)
Multivariable-adjusted model 2†	1.0 (referent)	0.55 (0.25–1.22)	0.43 (0.22–0.83)	0.56 (0.26–1.22)	0.75 (0.36–1.53)

* Adjusted for age, smoking (number of cigarettes smoked per day), body mass index, diabetes, valvular heart disease, and hypertension.
† Adjusted for high-density lipoprotein cholesterol level in addition to variables included in model 1.

In men who consumed 42 drinks/wk or more, 3 cases of congestive heart failure occurred during 752 person-years of follow-up. In women who consumed 28 drinks/wk or more, 2 cases of congestive heart failure occurred during 364 person-years of follow-up. After adjustment for age, smoking, body mass index, diabetes, valvular heart disease, and hypertension, the hazard ratio for congestive heart failure was 0.6 (95% CI, 0.2 to 2.1) in men who consumed 42 drinks/wk or more and 2.0 (CI, 0.5 to 8.7) in women who consumed 28 drinks/wk, compared with nondrinkers.

In men, the age-adjusted incidence of death from noncardiovascular causes was 15.4 deaths/1000 person-years (CI, 11.3 to 19.6 deaths/1000 person-years) in nondrinkers and 10.9 deaths/1000 person-years (CI, 8.1 to 13.8 deaths/1000 person-years) in men who consumed 15 drinks/wk or more. In women, the age-adjusted incidence of death from noncardiovascular causes was 9.3 deaths/1000 person-years (CI, 7.3 to 11.2 deaths/1000 person-years) in nondrinkers and 10.0 deaths/1000 person-years (CI, 6.8 to 13.1 deaths/1000 person-years) in women who consumed 8 drinks/wk or more.

Alcohol Consumption and Risk for Congestive Heart Failure without Preceding Myocardial Infarction

During follow-up, 162 myocardial infarctions occurred in men and 102 myocardial infarctions occurred in women. In men, 71 cases of congestive heart failure (72% of all cases) occurred without preceding myocardial infarction during 25 802 person-years. In women, 85 cases of congestive heart failure (71% of all cases) occurred without preceding myocardial infarction during 35 456 person-years. Table 4 shows the age-adjusted incidence of congestive heart failure without preceding myocardial infarction in men and women, by level of alcohol consumption.

Risk for congestive heart failure without preceding myocardial infarction was reduced among men who

Table 6. **Risk for Congestive Heart Failure in Women, by Level of Alcohol Consumption**

Disease	Hazard Ratio (95% CI)				
	Nondrinkers	Former Drinkers	1–2 Drinks/wk	3–7 Drinks/wk	≥8 Drinks/wk
All-cause congestive heart failure					
Age-adjusted model	1.0 (referent)	1.06 (0.66–1.70)	0.73 (0.43–1.24)	0.49 (0.25–0.96)	0.81 (0.45–1.48)
Multivariable-adjusted model 1*	1.0 (referent)	1.11 (0.69–1.78)	0.77 (0.45–1.30)	0.53 (0.27–1.03)	0.80 (0.44–1.46)
Multivariable-adjusted model 2†	1.0 (referent)	1.15 (0.72–1.86)	0.82 (0.48–1.39)	0.60 (0.31–1.18)	1.04 (0.56–1.92)
Congestive heart failure without preceding myocardial infarction					
Age-adjusted model	1.0 (referent)	0.86 (0.47–1.59)	0.98 (0.55–1.76)	0.51 (0.23–1.11)	0.84 (0.41–1.70)
Multivariable-adjusted model 1*	1.0 (referent)	0.91 (0.50–1.69)	1.07 (0.60–1.90)	0.55 (0.25–1.20)	0.83 (0.41–1.70)
Multivariable-adjusted model 2†	1.0 (referent)	0.95 (0.51–1.75)	1.13 (0.63–2.01)	0.60 (0.27–1.33)	1.02 (0.49–2.10)

* Adjusted for age, smoking (number of cigarettes smoked per day), body mass index, diabetes, valvular heart disease, and hypertension.
† Adjusted for high-density lipoprotein cholesterol level in addition to variables included in model 1.

consumed 1 to 7 drinks/wk compared with nondrinkers after adjustment for multiple predictors of congestive heart failure, including HDL cholesterol level (**Table 5**). In women, no association was seen between alcohol consumption and risk for congestive heart failure without preceding myocardial infarction (**Table 6**). Men and women in the highest categories of alcohol consumption (≥15 drinks/wk and ≥8 drinks/wk, respectively) had no greater risk for congestive heart failure without preceding myocardial infarction than did nondrinkers.

DISCUSSION

In our community-based sample, risk for congestive heart failure was lower among men at all levels of alcohol consumption compared with nondrinkers, before and after adjustment for multiple predictors of congestive heart failure. The lowest hazard ratio for congestive heart failure was seen in men who consumed 8 to 14 drinks/wk. The observed association between alcohol consumption and risk for congestive heart failure in men was not affected by adjustment for hypertension, but it was mildly attenuated by adjustment for HDL cholesterol. Among women, age-adjusted risk for congestive heart failure was lower among women who consumed 3 to 7 drinks/wk than in nondrinkers. This association remained marginally statistically significant after adjustment for multiple predictors of congestive heart failure. No level of alcohol consumption in men or women was associated with increased risk for congestive heart failure.

Alcohol Consumption and Left Ventricular Function

Case series (1) and case–control studies (2, 3, 35) have found a high prevalence left ventricular dysfunction among asymptomatic persons who consume large quantities of alcohol (>5 drinks/d). In community-based samples that consume less alcohol, cross-sectional studies have demonstrated only modest associations between alcohol consumption and subclinical abnormalities of left ventricular structure and function (9, 36). In the Framingham Heart Study sample, Manolio and colleagues found an association between alcohol consumption and echocardiographic left ventricular mass in men but not women (9). In men, alcohol intake was related to both left ventricular hypertrophy and left ventricular dilation, and this association was independent of systolic blood pressure. Kupari and Koskinen (36) studied the effects of alcohol consumption on echocardiographic left ventricular function in 93 persons without coronary heart disease who were drawn randomly from the population. Alcohol intake was not associated with left ventricular mass but was associated with increased left ventricular systolic dimension and reduced fractional shortening.

Alcohol Consumption, Coronary Heart Disease, and Congestive Heart Failure

Numerous large, prospective cohort studies have found that moderate alcohol consumption is associated with reduced risk for coronary heart disease and myocardial infarction (11–14). Myocardial infarction, in turn, is an important precursor of congestive heart failure (15–18). Protective effects of moderate alcohol intake against myocardial infarction may offset any potential negative effect of alcohol on ventricular function. Consistent with this hypothesis, Cooper and associates (37) reported that light to moderate alcohol consumption was not associated with increased risk for congestive heart failure progression among patients with ischemic left ventricular systolic dysfunction, but it was associated with a trend toward increased risk for hospitalization for congestive heart failure in patients with nonischemic left ventricular systolic dysfunction. Thus, protective effects of alcohol consumption against coronary heart disease may account for the inverse association between alcohol consumption and congestive heart failure that we observed.

Moderate alcohol consumption increases serum levels of HDL cholesterol (38). High-density lipoprotein cholesterol has been estimated to account for approximately 50% of the protective effect of alcohol against coronary heart disease (39, 40). Adjustment for HDL cholesterol level in our study slightly attenuated the inverse association between moderate alcohol consumption and risk for congestive heart failure in men. This suggests that part of the protective effect of alcohol against congestive heart failure may be related to an alcohol-mediated increase in serum HDL cholesterol levels.

If alcohol consumption protects against congestive heart failure primarily by preventing myocardial infarction, the lower risk for congestive heart failure among drinkers would be expected to result from a lower risk for myocardial infarction. Conversely, risk for congestive heart failure in the absence of myocardial infarction would be expected to be nearly the same among both drinkers and nondrinkers. To test this hypothesis, we repeated our analysis after censoring participants with interim myocardial infarction. We found that risk for congestive heart failure without preceding myocardial infarction was significantly reduced in men in the lowest alcohol intake category (1 to 7 drinks/wk) compared with nondrinkers. Relatively few end points were available for this secondary analysis, and we had limited statistical power. Nonetheless, for men in the highest drinking categories, the risk for congestive heart failure without preceding myocardial infarction was similar to those for all-cause congestive heart failure. Our data are consistent with those of previous reports (41) showing that a lower risk for myocardial infarction among drinkers does not entirely explain the inverse association between moderate alcohol consumption and risk for congestive heart failure.

Heavy Alcohol Consumption and Risk for Congestive Heart Failure

Chronic, excessive alcohol consumption has been proposed as a major cause of cardiomyopathy in industrialized countries, such as the United States (42, 43). In our sample, 23% of men consumed 15 drinks/wk or more and 17% of women consumed 8 drinks/wk or more, levels of alcohol consumption that are considered by the National Institute of Alcohol Abuse and Alcoholism to constitute heavy drinking (25). At this level of alcohol consumption, we observed no increased risk for congestive heart failure compared with nondrinkers. In fact, among men who consumed 15 drinks/wk or more (mean alcohol consumption, 27.3 drinks/wk), the multivariable-adjusted risk for congestive heart failure was significantly reduced compared with nondrinkers (hazard ratio, 0.52 [CI, 0.28 to 0.96]). This was particularly surprising, given that people may underreport alcohol consumption because of the social stigma associated with excessive drinking.

It is possible that alcohol-mediated cardiomyopathy occurs only at higher levels of alcohol consumption than observed in our study sample, or that it may require coexisting malnutrition or genetic predisposition. In addition, because heavy drinkers have increased mortality from cirrhosis, injuries, violence, suicide, and certain cancers (11), they may die before they clinically manifest alcohol-related cardiomyopathy. However, in our sample, the age-adjusted incidence of death from noncardiovascular causes in participants in the highest categories of alcohol consumption was similar to that in nondrinkers, suggesting that our findings are not a result of an excess of deaths due to alcohol-related illnesses among heavy drinkers.

Alcohol Consumption, Hypertension, and Congestive Heart Failure

Although heavy alcohol consumption is an important cause of hypertension, moderate alcohol consumption appears to have at most a modest effect on blood pressure (8, 44). In our study, controlling for hypertension did not affect the inverse association between moderate alcohol consumption and risk for congestive heart failure, suggesting that alcohol intake at the levels observed in our study contributes little to hypertension-mediated myocardial dysfunction. At higher levels of consumption, protective effects of alcohol against coronary heart disease may be offset by alcohol-related hypertensive heart disease.

Sex Differences in the Association of Alcohol Consumption and Congestive Heart Failure

Among men, drinkers had a lower risk for congestive heart failure than did nondrinkers. Although we observed a reduction in the age-adjusted risk for congestive heart failure among women who consumed 3 to 7 drinks/wk compared with nondrinkers, this association was only marginally statistically significant after adjustment for multiple predictors of congestive heart failure.

Some (45–47) but not all (36) studies have reported sex-related differences in the response of the myocardium to alcohol. Studies of alcoholic persons without overt cardiomyopathy (45, 46) have had conflicting results regarding the differential effects of alcohol on ventricular function in men and women. Wu and colleagues (45) reported that subclinical abnormalities of ventricular systolic function are more common in men than women at comparable levels of alcohol consumption. In contrast, Urbano-Márquez and colleagues (46) reported that women develop ventricular systolic dysfunction at lower levels of alcohol consumption compared with men, and Fernández-Solà and associates (47) found that women develop alcoholic cardiomyopathy at a lower total lifetime dose of alcohol compared with men.

Data are sparse on sex-specific differences in the association between alcohol consumption and risk for congestive heart failure at the more modest levels of alcohol intake commonly encountered in the community. In our study, the inverse association between alcohol consumption and risk for congestive heart failure was less pronounced in women than men. It is possible that women are susceptible to alcohol-mediated ventricular dysfunction at relatively low levels of alcohol intake, thereby diminishing the potentially protective effects of alcohol against congestive heart failure.

Limitations

First, we relied on self-reporting of alcohol intake, which may result in misclassification of exposure status. Random misclassification would be expected to weaken the observed association of alcohol consumption with risk for congestive heart failure and bias our results toward the null. Alternatively, selective misclassification of heavy drinkers as nondrinkers may account for the increased risk for congestive heart failure seen among participants who reported no alcohol intake. This is unlikely, however, because we observed a positive association between alcohol consumption and HDL cholesterol level in both men and women, a finding that supports the rank-order validity of self-reported alcohol intake. Second, we did not adjust for drinking pattern and beverage type. Alcohol consumption patterns (for example, binge drinking versus regular alcohol consumption) and type of beverage consumed (beer, wine, or spirits) may affect risk for congestive heart failure independently of total alcohol intake. Third, alcoholic cardiomyopathy may occur at a relatively young age. If so, the heaviest drinkers may have developed congestive heart failure before entry into our study. Finally, nondrinkers, who served as the reference group in our study, may include both lifelong abstainers and former drinkers. Former drinkers may be at increased risk for cardiovascular disease relative to mild to moderate drinkers, potentially obscuring deleterious effects of alcohol consumption on risk for congestive heart failure. We attempted to account for this by using as our reference group only participants who reported consuming less than 1 drink/wk at both the index examination and an examination 6 to 10 years before the index examination. Risk for congestive heart failure in former drinkers did not differ significantly from that in nondrinkers in our study.

Our findings should be interpreted with caution. We excluded persons with congestive heart failure at baseline, and our results therefore do not apply to persons with existing congestive heart failure. In addition, although we found no increase in risk for congestive heart failure among participants in the highest categories of alcohol intake, other studies have shown increased overall mortality due to alcohol-related illnesses among persons reporting similar levels of alcohol consumption (11). Recommendations by health professionals regarding alcohol consumption should take into account the overall health effects of alcohol.

In conclusion, in our community-based sample, alcohol was not associated with increased risk for congestive heart failure among persons with heavy alcohol consumption (≥15 drinks/wk in men and ≥8 drinks/wk in women) and was associated with a lower risk for congestive heart failure when consumed in moderation. Accounting for the effects of alcohol on risk for myocardial infarction did not entirely explain the apparent protective effects of alcohol against congestive heart failure.

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"They flee from me that sometime did me seek. . . ."
—Thomas Wyatt

The urban birds are in frantic flight again
As they careen from roof to roof, alighting
On the occasional lamppost, and then
Regaining the flock for a fresh sighting.
These birds that now are in such disarray
Used to tarry and "take bread at my hand,"
Used to puff themselves up, parry and play,
Their soft wings shaking, used to strut and stand.
And now they flee, as swift as time itself
And as fleeting—is it something in the air,
A breath of winter urgency and stealth
That stirs them so—ecstasy or despair?
Now see them come to rest, like calming words
After a death—these wings, these urban birds.

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The Effect of Controlled Drinking in Alcoholic Cardiomyopathy

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Background: **Cardiomyopathy is a potentially fatal complication of alcohol abuse. In alcoholic persons who develop cardiac dysfunction, abstinence is thought to be essential to halt further deterioration of cardiac contractility. Some evidence indicates that reducing alcohol intake may also be beneficial.**

Objective: **To evaluate the effect of moderate "controlled" drinking on cardiac function in patients with alcoholic cardiomyopathy.**

Design: **4-year prospective cohort study.**

Setting: **A university hospital in Barcelona, Spain.**

Patients: **55 alcoholic men with cardiomyopathy who had been drinking a minimum of 100 g of ethanol per day for at least 10 years.**

Measurements: **Evaluation of ethanol intake and nutrition, clinical assessment of cardiac status, and sequential echocardiography and radionuclide cardiac angiography.**

Results: **After the first year of evaluation, all patients with cardiomyopathy who abstained from alcoholic beverages demonstrated significant improvement in left ventricular function (average increase in left ventricular ejection fraction, 0.131 [95% CI, 0.069 to 0.193]). Patients who drank 20 to 60 g of ethanol per day showed a comparable mean improvement of 0.125 (CI, 0.082 to 0.168). In contrast, left ventricular ejection fraction deteriorated further in most patients who continued to abuse alcohol (>80 g/d). After 4 years, left ventricular ejection fraction had continued to improve in both abstinent patients and those who controlled their drinking. Ten patients who had continued to consume more than 80 g of ethanol per day died during the study.**

Conclusion: **In patients with alcoholic cardiomyopathy, both abstinence and controlled drinking of up to 60 g of ethanol per day (four standard drinks) were comparably effective in promoting improvement in cardiac function.**

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See related article on pp 181-191 and editorial comment on pp 247-249.

Alcoholic cardiomyopathy is a complication of longstanding alcohol abuse and is related to a person's total lifetime dose of ethanol (1, 2). The malady is not uncommon; in developed countries, it accounts for 3% to 40% of all cases of dilated cardiomyopathy (3–6). In our previous studies, one third of asymptomatic alcoholic persons showed some evidence of cardiac dysfunction (1, 2, 7). Although the natural course of chronic alcoholic cardiomyopathy is not precisely defined, abstinence from alcohol has been reported to improve cardiac function, or at least halt its deterioration (8–10).

The treatment of alcoholic cardiomyopathy is generally assumed to require abstinence (11), and any further alcohol intake is thought to be deleterious. Yet abstinence is not always possible, and a sizable proportion of persons treated for alcoholism report that they are able to drink moderately (12). We therefore designed a 4-year prospective cohort study of patients with alcoholic cardiomyopathy. Although total abstinence was urged for all patients at the initial interview and on subsequent occasions, fewer than one third stopped drinking completely. A similar number maintained a controlled drinking pattern, and the remainder continued to abuse alcohol. We evaluated the effect of "controlled" drinking, defined as a daily intake of 20 to 60 g of alcohol per day (one to four standard drinks), in patients with alcoholic cardiomyopathy.

METHODS

Patient Selection

All patients were younger than 60 years of age and reported consuming more than 100 g of ethanol per day for at least 10 years. Over a 6-year period, 51 alcoholic patients were admitted to the cardiology unit or the emergency department of Hospital Clínic, Barcelona, Spain, with signs or symptoms of heart failure (New York Heart Association [NYHA] functional class II to IV) (13), left ventricular ejection fraction of 0.5 or less, and no evidence of any heart disease other than dilated cardiomyopathy. Alcoholic cardiomyopathy was diagnosed in all of these patients, and they were consecutively recruited for the study. Fifteen patients who presented to the outpatient alcoholism unit during the same period for assistance in terminating their depen-

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dence on alcohol, displayed cardiac enlargement on radiography, and were found to have alcoholic cardiomyopathy (left ventricular ejection fraction < 0.5) were also included in the study. The cardiothoracic index was abnormally large in all patients (≥ 0.5). In addition, all but 4 of the patients had an end-diastolic diameter greater than 2 standard deviations above that of a group of healthy volunteers.

Of the 66 alcoholic persons initially evaluated, 11 were excluded. Five had severe withdrawal symptoms, 1 reported cocaine use, and 1 was infected with HIV. Two patients with evidence of coronary artery disease were not considered good candidates for the study. Two patients had such severe alcoholic cardiomyopathy (ejection fraction < 0.1) that they died shortly after admission. Thus, a total of 55 patients with alcoholic cardiomyopathy remained in the study. No patients objected to inclusion, and all gave informed consent for the various procedures. The Institutional Review Board of Hospital Clínic approved the study protocol.

All patients were white men of Spanish descent who lived with their families in or around Barcelona and had histories of stable employment. Most were skilled laborers or office workers, and none were indigent. As part of our standardized program designed to terminate dependence on alcohol, all patients were repeatedly urged to become abstinent. The proportion of patients who stopped drinking was similar to that reported by others (12, 14).

To assess the normal variability of cardiac function over time, we also evaluated 10 healthy men (median age, 45 years [range, 35 to 45 years]) who reported drinking less than 20 g of ethanol per day. It is important to note that alcoholic beverages are part of Spanish culture and that total abstention from alcohol is uncommon. The controls were studied at the beginning and end of the study in the same manner as the men with alcoholism.

Clinical Studies

One of two physicians obtained a detailed history of ethanol intake for each patient using repeated interviews and a validated structured questionnaire (15, 16). In our experience, intra- and interobserver reliability of this type of assessment are greater than 90%. Data were confirmed by consultation with family members. Minor discrepancies in alcohol intake were found in five cases (9%), which were resolved by further consultation with the patients and their families. Frequency and amount of daily ethanol intake since patients began drinking habitually were recorded. Life events, such as marriage, military service, and work posts, were used as "anchor points" to help recollection (time-line follow-back method [15]). The total lifetime dose of ethanol was estimated by multiplying the amount of ethanol consumed per day by the number of years of each alcohol intake period multiplied by 365 and adding the total amounts ingested during these different periods (1, 7). Withdrawal symptoms were evaluated according to the Clinical Institute for Withdrawal Assessment Scale (17).

Laboratory and Nutritional Studies

Blood samples for laboratory tests were obtained the day after admission. Overall nutrition was assessed in terms of the proportion of actual weight to ideal weight. The lean body mass and muscular area of the arm were calculated from the circumference of the upper nondominant arm and the thickness of the tricipital skin fold, respectively. The fatty area of the arm, calculated from the thickness of the tricipital fold, was considered indicative of total body fat (1, 18). Body mass index was determined as the body weight relative to the square of the body height (kg/m^2). Patients were considered to have caloric malnutrition if their body weight was less than 80% of their ideal weight or if the calculated lean body mass was more than 10% below the control value. Protein malnutrition was diagnosed when patients had abnormally low values for three of the following: hemoglobin, lymphocyte count, total protein level, albumin level, prealbumin level, retinol-binding protein level, or transferrin level (18, 19). Hepatic ultrasonography was performed in all patients. Percutaneous needle biopsies of the liver were performed when serum aminotransferase levels remained elevated to more than twice the normal values for more than 2 months or when ultrasonography showed liver abnormalities.

Cardiac Studies

Past and present signs and symptoms of heart failure were evaluated, and NYHA functional class was determined according to the Goldman activity scale (13). Three days after admission, when results of tests for blood alcohol were uniformly negative, chest radiogra-

Table 1. **Baseline Epidemiologic, Nutritional, and Clinical Characteristics of 55 Alcoholic Men with Cardiomyopathy***

Characteristic	Value
Age, *y*	48.1 ± 7.3
Daily ethanol intake, *g*	208 ± 56
Duration of alcoholism, *y*	26.6 ± 7.3
Lifetime dose of ethanol, *kg/kg body of weight*	26.1 ± 8.1
Proportion of ideal body weight, %	101.7 ± 17.6
Lean body mass, *kg*	51.3 ± 4.5
Body mass index, *kg/m*^{2}	24.2 ± 4.6
Tricipital skin fold, *mm*	10.8 ± 5.9
Fat area of the arm, *cm*^{2}	11.0 ± 5.1
Hemoglobin level, *g/L*	141 ± 15
Lymphocyte count, ×10^6 *cells/L*	1881 ± 661
Total protein level, *g/L*	70.8 ± 7.3
Albumin level, *g/L*	40.8 ± 6.6
Prealbumin level, *mg/dL*	26.4 ± 11.0
Retinol-binding protein level, *mg/dL*	5.2 ± 2.2
Transferrin level, *mg/dL*	250 ± 51
NYHA functional class, *n (%)*	
Class I	11 (20)
Class II	13 (24)
Class III	18 (32)
Class IV	13 (24)
Cardiothoracic index	0.53 ± 0.02

* Data expressed with a plus/minus sign are the mean ± SD. NYHA = New York Heart Association.

phy, conventional electrocardiography, bidimensional echocardiography (Toshiba SS-10 instrument, Otawara, Japan), and technetium-99 radionuclide angiocardiography (Picker-Dyna 4-15 gamma-camera, Haifer, Israel) were performed. End-diastolic and end-systolic diameters, the shortening fraction, and the mass of the left ventricle were measured according to the standards of the American Society of Echocardiography (20). Values for left ventricular ejection fraction were obtained by using isotopic angiography, which is reported to be a reliable method (1, 2, 21). The personnel who performed and evaluated these tests had no knowledge of the alcoholic history of the patients. To rule out ischemic heart disease, patients underwent a treadmill electrocardiographic test.

At the end of the first year and annually thereafter for up to 4 years, interviews, laboratory tests, and clinical examinations were repeated for all patients. Ethanol consumption, pharmacologic treatment, and incidental disease were recorded at each interview. At the end of the first year of follow-up, patients were classified into one of four groups according to level of alcohol consumption: 1) complete abstinence; 2) controlled drinking of 20 to 60 g of ethanol per day, a range commonly accepted as moderate (22); 3) an indeterminate range of 60 to 80 g of ethanol per day; and 4) alcohol abuse, defined as more than 80 g of ethanol per day. For patients who died during follow-up, death was classified as cardiologic or noncardiologic.

Statistical Analysis

We used standard statistical methods from the SPSS Statistical Analysis System, version 9.0 (SPSS, Inc., Chicago, Illinois) (23). In each group of patients, we used the paired *t*-test when comparing variables from different time periods.

Role of the Funding Sources

The funding sources had no role in the design, analysis, or interpretation of the study or in the decision to submit the results for publication.

RESULTS

Clinical Characteristics

Patients with alcoholic cardiomyopathy ranged in age from 31 to 59 years. Alcoholic beverages were generally consumed continuously as part of everyday life, and no binge drinking was reported. Patients most often drank wine, beer, or brandy and less frequently drank anisette, whiskey, or gin. The mean daily ethanol intake was 208 g (range, 100 to 310 g) over 26.6 years (**Table 1**). The mean total lifetime dose of ethanol (26.1 kg/kg of body weight [range, 12 to 42 kg/kg]) was similar to that observed in previous studies (1, 2). Most of the patients (75%) had smoked one to two packs of cigarettes per day since the second decade of their lives. None of the patients used illicit drugs.

Nutritional Status and Laboratory Data

Nutritional and laboratory variables are shown in **Table 1**. Six patients exhibited mild caloric malnutrition, and 4 had slight protein malnutrition. Of the 28 patients who had liver biopsy, 3 had normal livers, 17 had cirrhosis, 6 had fatty liver, and 2 had mild alcoholic hepatitis. Among the 17 patients with cirrhosis, 6 had hepatitis C virus antibodies and 1 had antibodies against hepatitis B virus but was negative for surface antigen. None of the patients had signs or symptoms of liver failure; all were categorized as class A by Child–Pugh classification (24).

Initial Cardiac Status

At study entry, 24 patients were classified as NYHA functional class I to II and 31 were classified as class III to IV (**Table 1**). Electrocardiographic studies showed atrial fibrillation in 14 patients, conduction defects in 12, and premature ventricular contractions in 17. All patients had abnormally elevated end-diastolic and end-systolic diameters and left ventricular mass. They also had abnormally low left ventricular shortening fractions and ejection fractions (**Table 2**). All patients were normotensive (mean blood pressure [±SD], 127 ± 14/77 ± 14 mm Hg). During the study, patients were treated according to NYHA functional class. In addition to ethanol abstinence, we recommended a dietary sodium intake of less than 100 mmol/d for all patients. Patients who had NYHA class II to IV disease ($n = 44$) were treated with an angiotensin-converting enzyme inhibitor (captopril, 25 to 50 mg three times per day) according to individual tolerance. In addition, 18 patients who had NYHA class III to IV disease and presented with congestive heart failure received furosemide (20 to 40 mg twice per day) and spironolactone (25 to 50 mg/d). Eleven patients with atrial fibrillation also received digoxin (0.25 mg/d). No patient was treated with β-blockers or hydralazine during the study.

Table 2. **Left Ventricular Function at Study Entry in Patients with Alcoholic Cardiomyopathy and in Healthy Volunteers***

Variable	Patients with Alcoholic Cardiomyopathy ($n = 55$)	Healthy Volunteers ($n = 10$)
End-diastolic diameter, *mm*	62.2 ± 8.9	48.0 ± 1.9
End-diastolic diameter index, *mm/m²*	33.9 ± 5.2	27.7 ± 1.2
End-systolic diameter, *mm*	45.8 ± 11.3	30.3 ± 4.2
End-systolic diameter index, *mm/m²*	24.9 ± 5.9	17.4 ± 2.4
Shortening fraction, *%*	26.5 ± 8.2	38.2 ± 7.2
Left ventricular mass, *g*	280 ± 99	183 ± 36
Left ventricular mass index, *g/m²*	153 ± 51	106 ± 22
Ejection fraction	0.393 ± 0.113	0.667 ± 0.049

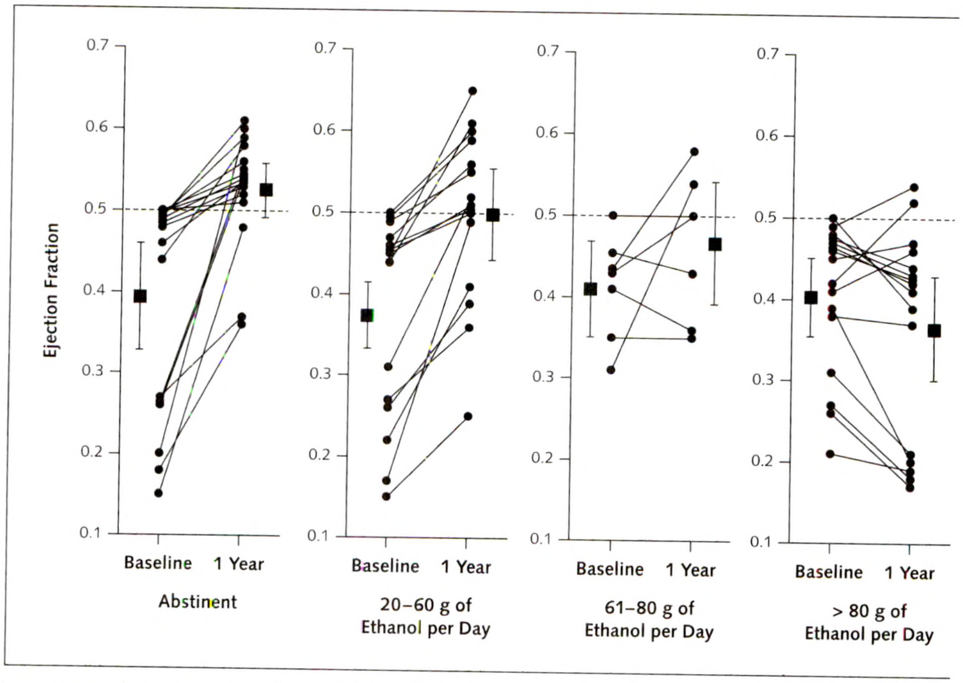
* Data are expressed as the mean ± SD. End-diastolic and end-systolic diameters, shortening fraction, and left ventricular mass were measured according to the standards of the American Society of Echocardiography (20). Left ventricular ejection fraction was obtained by isotopic angiography.

First-Year Follow-up Studies

Ethanol Consumption

During the first year of the study, 17 patients stopped drinking entirely, 15 reduced their ethanol in-

Figure. **Changes in left ventricular ejection fraction in patients with alcoholic cardiomyopathy, according to daily ethanol intake during the first year of the study.**



Group values (*squares*) are expressed as means; error bars represent 95% CIs.

Table 3. **Changes in Cardiac Function at 1-Year Follow-up, according to Alcohol Consumption***

Variable	Abstinent (n = 17)			20 to 60 g of Ethanol per Day (n = 15)		
	Baseline	1 Year	Mean Difference (95% CI)	Baseline	1 Year	Mean Difference (95% CI)
End-diastolic diameter, *mm*	60.8 ± 11.1	56.7 ± 6.8†	−4.1 (−7.6 to −0.6)	63.0 ± 8.5	59.4 ± 7.8‡	−3.5 (−5.6 to −1.4)
End-diastolic diameter index, mm/m^2	32.9 ± 6.1	30.7 ± 3.4†	−2.2 (−4.1 to −0.3)	33.1 ± 4.9	31.2 ± 4.5‡	−1.8 (−2.9 to −0.7)
End-systolic diameter, *mm*	44.2 ± 11.8	38.9 ± 4.6†	−5.3 (−10.1 to −0.5)	48.2 ± 11.7	42.8 ± 9.6‡	−5.3 (−8.5 to −2.8)
End-systolic diameter index, mm/m^2	23.9 ± 6.0	21.0 ± 2.5†	−2.9 (−5.4 to −0.3)	25.2 ± 5.8	22.4 ± 4.9‡	−2.7 (−4.4 to −1.0)
Shortening fraction, %	27.3 ± 7.1	30.7 ± 5.0†	3.3 (0.2 to 6.5)	24.2 ± 10.8	29.9 ± 6.7†	5.2 (1.4 to 8.9)
Left ventricular mass, *g*	280 ± 108	248 ± 60	−32 (−68.5 to 4.5)	293 ± 80	261 ± 59	−32 (−66.3 to 2.3)
Left ventricular mass index, g/m^2	151 ± 56	131 ± 28†	−20 (−39.5 to −0.4)	153 ± 39	136 ± 30†	−17 (−34.2 to 0.1)
Ejection fraction	0.394 ± 0.135	0.525 ± 0.068§	0.131 (0.069 to 0.193)	0.374 ± 0.127	0.499 ± 0.107§	0.125 (0.082 to 0.168)

* Data expressed with a plus/minus sign are the mean ± SD.
† $P < 0.05$ when compared with baseline for each group (paired t-test).
‡ $P < 0.01$ when compared with baseline for each group (paired t-test).
§ $P < 0.001$ when compared with baseline for each group (paired t-test).

take to 20 to 60 g/d, 7 consumed 61 to 80 g/d, and 16 continued to drink more than 80 g/d. The level of ethanol consumption remained stable during the first year. Since alcoholic persons do not tend to exaggerate and often underreport the amount they continue to drink, we consider these reports to be minimal estimates. This modification of ethanol intake was similar to that observed in other studies (12, 14) and correlated with changes in γ-glutamyl transpeptidase levels. Even patients who continued to drink heavily reduced their alcohol consumption substantially. Among those who persisted in consuming more than 80 g of ethanol per day, the mean daily intake (±SD) decreased from 221 ± 51 g to 150 ± 38 g in the first year of follow-up. Nutritional, caloric, and protein variables did not differ at baseline among the four groups.

Cardiac Studies

Baseline cardiac status and therapy during the first year of follow-up were similar among the four groups of patients. During the first year of follow-up, 7 of the 17 patients who abstained from alcohol received only captopril and 6 were treated with captopril plus diuretics. Of the 15 patients who controlled their ethanol intake, 6 were treated with captopril and 6 were given captopril plus diuretics. In the group of patients who consumed 61 to 80 g of ethanol per day, 6 received treatment with captopril, 1 of them in addition to diuretics. Eight patients who continued drinking more than 80 g/d were treated with captopril, and 5 received captopril plus diuretics. Two patients who drank 60 to 80 g of ethanol per day and 3 patients in each of the other groups were treated with digoxin. All patients adhered to recommended drug regimens during the first year of follow-up, and no patients died during this period.

By the end of first year of follow-up, left ventricular function improved in all abstinent patients (mean increase in left ventricular ejection fraction, 0.131 [CI, 0.069 to 0.193]) (**Table 3**, **Figure**). The most important and unexpected finding was related to moderate or "controlled" alcohol consumption, defined as 20 to 60 g/d (22). Cardiac contractility improved in all 15 patients with alcoholic cardiomyopathy who controlled their alcohol consumption. The mean increase in left ventricular ejection fraction was 0.125 (CI, 0.082 to 0.168), which is close to the increase seen in patients who abstained from alcohol (**Table 3**). Patients who drank at an intermediate level, defined as 61 to 80 g/d, had mixed results. As expected, left ventricular ejection fraction deteriorated further in most patients who continued to abuse alcohol (>80 g/d) (mean decrease, −0.038 [CI, −0.001 to −0.075]). Of interest, in this group, 4 patients who continued to drink heavily but had reduced their alcohol intake by approximately 50% actually demonstrated a functional improvement. End-diastolic and end-systolic diameters, left ventricular mass, and the shortening fraction also improved in patients who abstained from alcohol and those who drank moderately (**Table 3**). Indices of left ventricular function remained unchanged in healthy volunteers during the follow-up period.

As reported elsewhere (1, 25), age, nutrition, and the presence of cirrhosis did not influence the changes in functional measures. No significant changes in blood

Table 3—**Continued**

61 to 80 g of Ethanol per Day ($n = 7$)			>80 g of Ethanol per Day ($n = 16$)		
Baseline	**1 Year**	**Mean Difference (95% CI)**	**Baseline**	**1 Year**	**Mean Difference (95% CI)**
63.1 ± 4.5	61.5 ± 3.3	−1.6 (−4.7 to 1.4)	62.3 ± 8.9	61.0 ± 11.9	−1.3 (−3.7 to 1.1)
33.4 ± 3.8	32.5 ± 2.3	−0.9 (−2.5 to 0.6)	37.2 ± 6.0	36.4 ± 7.5	−0.8 (−2.3 to 0.7)
46.0 ± 7.1	44.3 ± 6.5	−1.6 (−5.3 to 2.0)	45.5 ± 13.3	46.6 ± 14.3	1.0 (−1.1 to 3.1)
24.3 ± 3.8	23.3 ± 2.6	−0.9 (−2.9 to 0.9)	27.2 ± 8.3	27.9 ± 8.9	0.7 (−0.6 to 2.0)
27.1 ± 6.9	28.3 ± 7.2	1.1 (−3.3 to 5.6)	24.3 ± 8.2	25.0 ± 9.2	0.6 (−1.6 to 2.8)
285 ± 63	285 ± 60	0 (−34.2 to 34.2)	268 ± 84	260 ± 79	−8 (−46.9 to 30.9)
152 ± 42	151 ± 34	−1.4 (−19.4 to 16.6)	159 ± 50	155 ± 47	−4 (−25.3 to 17.3)
0.41 ± 0.07	0.467 ± 0.089	0.057 (−0.037 to 0.151)	0.403 ± 0.094	0.365 ± 0.128†	−0.038 (−0.075 to −0.001)

pressure were detected during the study. At the end of the first year of follow-up, NYHA functional class had improved in 9 patients who abstained from alcohol, 8 who reduced their ethanol intake to 20 to 60 g/d, 2 who consumed 61 to 80 g/d, and 2 who continued to drank heavily. Conversely, NYHA functional class worsened in 1 patient who drank 70 g/d and 4 patients who continued to drink heavily. We adjusted therapy according to NYHA functional class and the presence of congestive heart failure, as described earlier. Digoxin was withdrawn in 3 patients whose atrial fibrillation was reversed.

Long-Term Follow-up Studies

Patients were studied for 3 years after the initial 1-year follow-up. Left ventricular ejection fraction worsened in 6 alcoholic patients who were abstinent during the first year of the study but then relapsed and consumed more than 80 g of ethanol per day (mean decrease, 18.4% [CI, 9.9% to 26.9%]; $P = 0.007$). In contrast, left ventricular ejection fraction improved in 5 patients who drank more than 80 g/d for the first year and then became abstinent (mean increase, 13.2% [CI, 3.2% to 23.1%]; $P = 0.006$). Patients who drank 60 to 80 g of ethanol per day during follow-up tended to show a deterioration in left ventricular ejection fraction and a progressive increase in end-diastolic and end-systolic diameters. As expected, cardiac function decreased substantially in most patients who continued to drink more than 80 g of ethanol per day.

Because controlled drinking proved to be an effective way to improve left ventricular function during the first year, we examined whether such improvement was maintained during long-term follow-up (Table 4). Twelve alcoholic patients remained in the controlled

Table 4. **Cardiac Function in Healthy Volunteers and in Alcoholic Patients with Cardiomyopathy Who Drank Moderately***

Variable	Healthy Volunteers ($n = 10$)			Patients Consuming 20 to 60 g of Ethanol per Day ($n = 12$)		
	1 Year	4 Years	Mean Difference (95% CI)	1 Year	4 Years	Mean Difference (95% CI)
End-diastolic diameter, *mm*	57.6 ± 5.8	55.0 ±4.2†	−2.6 (−4.2 to −0.9)	60.3 ± 9.3	60.6 ± 11.0	0.3 (−3.5 to 4.1)
End-diastolic diameter index, *mm/m²*	31.3 ± 3.4	29.9 ±2.8†	−1.4 (−2.3 to −0.4)	31.7 ± 5.5	31.8 ± 5.8	0.1 (−1.8 to 2.0)
End-systolic diameter, *mm*	38.1 ± 3.9	36.8 ±3.9	−1.2 (−3.2 to 0.7)	44.2 ± 10.5	47.2 ± 12.4	3 (−0.8 to 6.8)
End-systolic diameter index, *mm/m²*	20.7 ± 2.2	20.0 ± 1.9	−0.6 (−1.6 to 0.4)	22.8 ± 6.1	24.3 ± 6.4	1.4 (−0.5 to 3.4)
Shortening fraction, %	33.0 ± 5.0	34.6 ± 2.6	1.6 (−1.7 to 5.0)	29.0 ± 6.7	25.4 ± 6.8	−3.6 (−7.0 to −0.1)
Left ventricular mass, *g*	241 ± 32	248 ± 40	7 (−8.5 to 22.6)	276 ± 47	287 ± 77	11 (−28.3 to 51.7)
Left ventricular mass index, *g/m²*	130 ± 19	133 ± 22	3 (−8.4 to 14.4)	143 ± 27	147 ± 34	4 (−15.8 to 24.8)
Ejection fraction	0.52 ± 0.063	0.619 ± 0.065†	0.096 (0.044 to 0.149)	0.474 ± 0.105	0.515 ±0.103†	0.041 (0.012 to 0.068)

* Data expressed with a plus/minus sign are the mean ± SD.

† $P < 0.01$ when compared with 1-year values for each group (paired *t*-test).

drinking group (20 to 60 g/d) for 3 additional years. Of these, left ventricular ejection fraction remained stable or improved further in 11 (mean increase, 0.041 [CI, 0.012 to 0.068]) and decreased by 0.02 in 1. This additional improvement in left ventricular ejection fraction was somewhat less than that observed in the long-term abstainers (mean increase, 0.096 [CI, 0.044 to 0.149]). At the end of the study, 2 patients who drank moderately but none of the patients who abstained continued to receive furosemide and captopril. After the 4-year study was completed, patients were followed for additional periods of 2 to 8 years. During this time, no patients had myocardial infarction or developed angina.

Mortality

No patients died in the first year of the study. Ten patients, all of whom continued to consume more than 80 g of ethanol per day after the first year of follow-up, died during the study. Seven patients died of end-stage heart disease, and 3 patients died of noncardiac diseases (hepatic failure, lung cancer, and pneumonia). Those who died of cardiac causes tended to show greater end-diastolic and end-systolic baseline indices and exhibited a progressive decrease in left ventricular ejection fraction and an increase in end-diastolic diameter.

DISCUSSION

It is generally agreed that the functional and morphologic characteristics of alcoholic cardiomyopathy do not differ from those of idiopathic dilated cardiomyopathy (26, 27). The diagnosis relies on the absence of known causes of dilated cardiomyopathy, the identification of excessive ethanol consumption, and an improvement in cardiac function after abstention from alcoholic beverages. As we (1–3) and others (28–32) have previously observed, long-term alcohol abuse leads to impairment of left ventricular function. In evaluations of alcohol-induced tissue damage, studies of the heart offer an advantage over those of other organs since the assessment of contractile function is a quantitative measure.

In our current study, cardiac function improved in all abstinent patients and deteriorated in a large proportion of those who did not change their drinking patterns. Contributory factors other than ethanol, such as differences in drug treatment during the study, were excluded. Compensated liver disease itself does not adversely influence cardiac function (25). No patients developed hypertension, and no evidence of ischemic heart disease was seen. We have followed more than 300 alcoholic patients for up to 10 years and have observed only 1 myocardial infarction and 1 case of angina. This situation probably reflects the protective effect of alcohol consumption on coronary artery disease (33).

Demakis and colleagues (10) showed that abstention from alcohol is associated with a more favorable clinical course in patients with alcoholic cardiomyopathy. In a more recent study, Guillo and associates (34) concluded that left ventricular ejection fraction improves in alcoholic persons with NYHA class IV heart failure if complete abstinence is accomplished. Perhaps because most of our patients consumed alcoholic beverages during the entire day and with meals rather than in patterns of binge drinking, more than a quarter chose to limit ethanol intake to 20 to 60 g/d rather than abstain completely. Of interest, after 1 year in the study, patients who limited their ethanol intake showed improvements in left ventricular function similar to those in patients who abstained. The left ventricular mass index at baseline was significantly higher in alcoholic patients than in the healthy volunteers, a finding similar to that in previous studies (1, 3, 28). Patients who abstained from alcohol and those who controlled their drinking both experienced a regression of left ventricular hypertrophy, a situation reminiscent of that observed after the control of hypertension (35) or the replacement of damaged heart valves (36). By the end of the study, left ventricular ejection fraction had remained stable or improved in almost all patients who controlled their drinking. No cardiac deaths were recorded among alcoholic patients who reduced their alcohol intake to a moderate level, whereas the total cardiac mortality rate was 41% after 5 years in those who continued to abuse alcohol (>80 g of ethanol per day). Survival analysis comparing the different groups was limited by the number of cases, individual drinking patterns, and duration of follow-up. Although continued ethanol abuse usually had a deleterious effect on cardiac function, we noted that cardiac function actually improved in several alcoholic patients who continued to consume more than 80 g of ethanol per day. Each of these patients had reduced his previous alcohol intake by more than 50%.

Our data provide preliminary evidence of a threshold for alcohol consumption, probably about 60 g/d (about four standard drinks), below which no damage is inflicted on the myocardium. A similar threshold has been suggested for alcoholic myopathy (37, 38) and alcoholic liver disease (39). Thus, in clinical practice, when cardiac function deteriorates in a presumably abstinent or near-abstinent alcoholic patient, the patient probably has another medical condition or is not being truthful about his or her alcohol consumption. It is noteworthy that not all patients with chronic alcoholism, even those who drink particularly large amounts of ethanol, develop cardiac dysfunction. A genetic component has been documented for idiopathic dilated cardiomyopathy (26), and we recently obtained preliminary evidence of a similar familial tendency in alcoholic cardiomyopathy (Unpublished data). Our current results, which show left ventricular improvement in alcoholic patients with dilated cardiomyopathy who converted to moderate drinking, should not be extrapolated to patients with other types of left ventricular dysfunction regardless of whether they have heart failure.

In summary, left ventricular function improved considerably in patients with alcoholic cardiomyopathy who achieved abstinence and to a similar extent in those who controlled their alcohol consumption. A larger study is needed to demonstrate key differences between groups (for example, whether patients who drink moderately survive longer than those who drink heavily). A management strategy recommending continued use of alcohol at a reduced level (as opposed to total abstinence) was not evaluated and cannot yet be advocated. Abstinence remains the cornerstone of any alcohol treatment program and continues to be recommended to all alcoholic patients with dilated cardiomyopathy.

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Dietary Patterns and Risk for Type 2 Diabetes Mellitus in U.S. Men

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Background: **The role of diet in the development of type 2 diabetes mellitus remains unsettled.**

Objective: **To examine the association between major dietary patterns and risk for type 2 diabetes mellitus.**

Design: **Prospective cohort study.**

Setting: **United States.**

Participants: **42 504 male health professionals, 40 to 75 years of age, without diagnosed diabetes, cardiovascular disease, or cancer at baseline.**

Measurements: **Using factor analysis based on data from food-frequency questionnaires, we identified and validated two major dietary patterns that we labeled "prudent" (characterized by higher consumption of vegetables, fruit, fish, poultry and whole grains) and "western" (characterized by higher consumption of red meat, processed meat, French fries, high-fat dairy products, refined grains, and sweets and desserts). Relative risks and 95% CIs were adjusted for potential confounders, including body mass index (BMI), physical activity, and cigarette smoking.**

Results: **During 12 years of follow-up (466 508 person-years), we documented 1321 cases of type 2 diabetes. The prudent dietary pattern score was associated with a modestly lower risk for type 2 diabetes (relative risk for extreme quintiles, 0.84 [CI, 0.70 to 1.00]). In contrast, the western dietary pattern score was associated with an increased risk for type 2 diabetes (relative risk, 1.59 [CI, 1.32 to 1.93]; $P < 0.001$ for trend). A high score for the western dietary pattern combined with low physical activity (relative risk comparing extreme quintiles of dietary pattern score and physical activity, 1.96 [CI, 1.35 to 2.84]) or obesity (relative risk for BMI ≥ 30 kg/m^2 vs. <25 kg/m^2, 11.2 [CI, 8.07 to 15.6]) was associated with a particularly high risk for type 2 diabetes.**

Conclusion: **Our findings suggest that a western dietary pattern is associated with a substantially increased risk for type 2 diabetes in men.**

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The prevalence of type 2 diabetes mellitus is rapidly increasing in the United States (1, 2) and worldwide (3). Ecologic studies (4), migration studies (4, 5), and analyses of secular trends (4, 6) suggest that adoption of a western diet may be associated with increased incidence of type 2 diabetes. However, these studies could not separate the effects of diet from those of other risk factors, such as obesity and physical activity.

Studies of the relation between diet and incidence of type 2 diabetes on an individual level have predominantly focused on intake of macronutrients and fiber (7). However, these dietary factors alone probably explain only part of the effect of diet on glucose metabolism. Other nutrients, additives, contaminants, and unknown compounds and the physical properties of foods and interactions between nutrients (for example, with respect to bioavailability) may play a role in the deterioration of glucose metabolism. Hence, the examination of effects of food consumption may be an important complementary approach. Recently, the analysis of patterns of food consumption by using factor analysis has emerged as a useful tool for elucidating relationships between diet and health (8–11). The overall dietary pattern may affect health more than individual foods and nutrients do. Furthermore, dietary patterns reflect the way foods are consumed in reality, which may provide insight into possibilities for dietary changes and may facilitate the translation of findings to public health recommendations. Recent dietary intervention studies have indicated that interventions focused on dietary patterns can decrease blood pressure (12) and reduce cardiovascular complications (13).

Data on dietary patterns and risk for type 2 diabetes are sparse. Although two cross-sectional studies of dietary patterns and diabetes have been conducted (11, 14), these studies incompletely controlled for confounding by other lifestyle factors. Therefore, we prospectively examined the association between major dietary patterns and risk for type 2 diabetes in a large prospective study of U.S. professional men with extensive, repeatedly obtained information on diet and other lifestyle factors.

METHODS

Participants

The Health Professionals Follow-up Study started in 1986, when 51 529 male health professionals (den-

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tists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists) completed a detailed mailed questionnaire on medical history, diet, and other potential risk factors for major diseases. The participants lived in all 50 U.S. states, were predominantly white, and were 40 to 75 years of age in 1986. We excluded from the current analysis 1595 men who did not satisfy the a priori criteria of reporting daily energy intake of 3.3 to 17.6 MJ (800 to 4200 kcal/24 h) and leaving fewer than 70 responses blank of the 131 food items on the diet questionnaire (<5% had >11 blanks). We also excluded men who reported having diabetes, cardiovascular disease (myocardial infarction, angina pectoris, coronary artery surgery, or stroke), or cancer (except nonmelanoma skin cancer) at baseline because having these diagnoses may affect diet or reporting of diet. After exclusions, the study sample comprised 42 504 men, who were followed for incidence of type 2 diabetes and other diseases for 12 years (1986 to 1998). Every 2 years, the participants received questionnaires by mail that asked for updated information on exposures and newly diagnosed diseases. The follow-up rate for potential person-years was about 97% for nonfatal events. We identified deaths by reports from family members, coworkers, or postal authorities or through systematic searches of the National Death Index.

Assessment of Dietary Patterns

To assess dietary intake, we used a 131-item semi-quantitative food-frequency questionnaire in 1986, 1990, and 1994. The questionnaire specified for each food a commonly used unit or portion size, and the participants were asked to indicate how often, on average, they had consumed a given amount of the specified food during the past year. Each such item provided nine possible responses, ranging from "never or less than once a month" to "6 or more times per day." To reduce within-respondent variation and to best represent long-term dietary habits, we averaged the dietary intakes from all available dietary questionnaires up to the start of each follow-up interval (the average of the 1986 and 1990 dietary intakes was related to incidence of type 2 diabetes between 1990 and 1994) (15).

To identify dietary patterns, we applied factor analysis to data from the food-frequency questionnaire. First, we grouped the food items on the questionnaire into 37 predefined food groups. We combined food items that were similar in nutrient profile and culinary use (for example, spinach, iceberg or head lettuce, and romaine or leaf lettuce were combined into "green leafy vegetables"). We classified a food item individually if its composition differed substantially from that of other foods (for example, eggs or pizza) or if we suspected that it represents a particular dietary habit (for example, wine or French fries).

Second, we applied the principal components program for factor analysis of SAS software (16) with varimax rotation to the 37 food groups. Factor analysis aggregates correlated variables. The obtained factors are linear combinations of the included variables, explaining as much of the variation in the original variables as possible. Our analysis retained two factors based on the eigenvalue of the factors, the Scree test, and the interpretability of the derived factors, and we labeled these diets as the "prudent" pattern and the "western" pattern (9).

Third, for each participant, we calculated a prudent pattern score and a western pattern score by summing the standardized intake of foods, weighted by the factor loadings of the foods (17). We used these scores to rank participants according to the degree to which they conformed to each dietary pattern. We divided dietary pattern scores into quintiles; thus, on this basis of his scores, each participant was grouped in a prudent-pattern quintile and a western-pattern quintile.

To test the validity and reproducibility of the assessment of the dietary pattern scores by the food-frequency questionnaire, we examined a subgroup of 127 participants (9). The Pearson correlation coefficient (corrected for week-to-week variation in the diet records) for a comparison between the responses to the food-frequency questionnaire and the diet records was 0.52 for the prudent dietary pattern and 0.74 for the western dietary pattern.

Assessment of Nondietary Exposures

The 1986 questionnaire and each biennial follow-up questionnaire assessed weight, smoking status, and physical activity. Participants provided information on age, diagnosis of hypertension and hypercholesterolemia, and height in 1986 and on family history of diabetes in 1987. The criterion for family history of type 2 diabetes was having at least one first-degree relative with a diagnosis of diabetes after 30 years of age. For each participant, we determined a physical activity level, measured in weekly metabolic equivalent hours, on the basis of reported time spent on various activities, which we weighted according to intensity level (18). The validity of self-reported weight (19) and physical activity (18) in this cohort has been reported previously.

Ascertainment of Type 2 Diabetes Mellitus

We mailed a supplementary questionnaire on symptoms, diagnostic tests, and medication use to participants who indicated on any biennial follow-up questionnaire that he had received a diagnosis of diabetes mellitus. Confirmation of diabetes required at least one of the following: 1) an elevated plasma glucose level (fasting plasma glucose level ≥ 7.8 mmol/L [≥140 mg/dL]; random plasma glucose level ≥ 11.1 mmol/L [≥200 mg/dL]; or plasma glucose level after 2 hours or more during an oral glucose tolerance test ≥ 11.1 mmol/L [≥200 mg/dL]) plus at least one classic symptom (excessive thirst, polyuria, weight loss, or hunger); 2) at least two elevated plasma glucose levels measured on different occasions; or 3) treatment with insulin or oral hypoglycemic medication. We excluded men who reported having type 1 diabetes on the supplementary questionnaire. These criteria for diabetes are consistent with those from the World Health Organization in 1985 (20). We did not use the current diabetes classification of the American Diabetes Association (21) because among the men in our study, most cases of diabetes were diagnosed before these criteria were published. The validity of our assessment of type 2 diabetes was verified with medical records in a subsample of 71 participants. A physician blinded to the information on the supplementary questionnaire reviewed the records according to the diagnostic criteria. Of the 71 participants classified as having type 2 diabetes, 12 had incomplete medical records—for example, absent laboratory data ($n = 2$) or only one set of laboratory data ($n = 9$). We confirmed the classification of type 2 diabetes in 57 (97%) of the other 59 other men in the subsample. One participant denied having diabetes, and another participant lacked evidence of diabetes in his submitted records.

Statistical Analysis

We used pooled logistic regression analyses with 2-year intervals to estimate the adjusted relative risk for each quintile compared with the lowest quintile of intake. With short time intervals and low rates of events, this approach gives results very similar to those of Cox proportional hazards analyses (22). Participants who died or received a diagnosis of diabetes during a 2-year cycle were censored at the end of that 2-year period and were not entered in any subsequent 2-year cycle. We used the cumulative average of available dietary assessments up to the start of each 2-year follow-up interval (15). We stopped updating a participant's dietary data at the beginning of the time interval during which he received a diagnosis of hypertension, hypercholesterolemia, cancer (except nonmelanoma skin cancer), or cardiovascular diseases, because subsequent changes in personal dietary habits could confound the relationship between diet and diabetes (15). Analyses using only dietary information from 1986 and analyses relating diet in 1986 to incidence of type 2 diabetes between 1992 and 1998 yielded essentially the same results.

To reduce residual confounding, the same cumulative updating approach was used for physical activity and alcohol intake by using the information of all available assessments. During follow-up, we also updated participant data on body mass index (BMI) and smoking status using the most recent data for each 2-year interval. We included categorical variables in the models as binary indicator variables. To further reduce extraneous variation or confounding due to variation in body size, physical activity, or metabolic efficiency or caused by over- or underreporting, we adjusted dietary pattern scores for total energy intake using the residual method (23). We tested for linear trends across categories of dietary intake by assigning each participant the median value for the category and modeling this value as a continuous variable. All P values reported are two sided.

Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the paper for publication.

RESULTS

Table 1 shows correlations between food intake and dietary pattern factors in 1986, 1990, and 1994. The correlation between a food and a factor increased as the contribution of that food to the corresponding dietary pattern score increased. The factor that we labeled the prudent dietary pattern was characterized by high consumption of vegetables, legumes, fruit, whole grains,

Table 1. **Pearson Correlation Coefficients for the Relationship between Food Intake and Factors Representing Dietary Patterns: Health Professionals Follow-up Study—1986, 1990, and 1994***

Foods	Correlation Coefficient					
	1986		1990		1994	
	Prudent Pattern	Western Pattern	Prudent Pattern	Western Pattern	Prudent Pattern	Western Pattern
Vegetables†	0.75	–	0.70	–	0.71	–
Dark-yellow vegetables	0.64	–	0.66	–	0.65	–
Cruciferous vegetables	0.63	–	0.66	–	0.63	–
Green leafy vegetables	0.63	–	0.63	–	0.63	–
Legumes	0.63	–	0.63	–	0.62	–
Fruit	0.60	–	0.62	–	0.58	–
Tomatoes	0.54	–	0.52	–	0.51	–
Fish	0.51	–	0.48	–	0.46	–
Whole grains	0.38	–	0.37	–	0.38	–
Poultry	0.36	–	0.35	–	0.32	–
Salad dressing‡	0.32	–	0.33	–	0.23	0.18
Fruit juice	0.32	–	0.32	–	0.30	–
Low-fat dairy products	0.16	–	0.17	–	0.19	–
Wine	–	–	–	–	–	–
Low-sugar drinks	–	–	–	–	–	–
Red meat	–	0.64	–	0.66	–	0.66
Processed meat	–	0.61	–	0.63	–	0.60
Refined grains	–	0.48	–	0.42	0.18	0.38
French fries	–	0.48	–	0.49	–	0.48
High-fat dairy products	–	0.47	–	0.52	–	0.50
Sweets and desserts	–	0.42	–	0.44	–	0.50
Eggs	–	0.42	–	0.48	–	0.46
Condiments	0.16	0.41	0.16	0.28	0.19	0.41
High-sugar drinks	–	0.36	–	0.35	–	0.32
Snacks§	–	0.36	–	0.33	–	0.33
Mayonnaise	–	0.34	–	0.36	–	0.35
Butter	–	0.34	–	0.36	–	0.37
Pizza	–	0.29	–	0.29	–	0.30
Margarine	–	0.29	–	0.30	–	0.34
Potatoes	0.26	0.29	0.31	0.26	0.33	0.29
Chowder or cream soup	–	0.22	–	0.24	–	0.31
Nuts	0.18	0.22	0.17	0.24	0.17	0.28
Coffee	–	0.27	–	0.23	–	0.23
Beer	–	0.16	–	–	–	0.15
Tea	–	–	–	–	–	–
Liquor	–	–	–	–	–	–
Organ meats	–	–	–	–	–	–

* With the orthogonal rotation used, correlations are identical to factor loading matrix; to simplify data presentation, loadings with an absolute value less than 0.15 are not shown. We used the same food groups as in previous analyses (10) except for "garlic" and "other soups," which were not included in the present study because intake of these foods was not assessed in 1990 or 1994, and "cold breakfast cereal," which was included in the whole-grains group (if ≥25% of weight consisted of whole grains or bran [24]) or the refined-grains group.

† Vegetables other than dark-yellow, cruciferous, or leafy-green vegetables.

‡ Salad dressing other than mayonnaise.

§ Potato or corn chips, crackers, popcorn.

fish, and poultry; the western dietary pattern was characterized by high consumption of red meat, processed meat, refined grains, French fries, high-fat dairy products, sweets and desserts, high-sugar drinks, and eggs.

The correlations between foods and factors representing dietary patterns were similar over time. Furthermore, the Pearson correlation between the prudent pattern score was 0.59 between 1986 and 1990, 0.60 between 1990 and 1994, and 0.55 between 1986 and 1994; for the western pattern scores, the Pearson correlation was 0.69 between 1986 and 1990, 0.72 between 1990 and 1994, and 0.64 between 1986 and 1994.

Table 2 shows the baseline characteristics of the study sample according to quintile of dietary pattern scores. On average, men with higher prudent-pattern scores were older, more physically active, less likely to be smokers, and more likely to have hypercholesterolemia. The cross-sectional association with hypercholesterolemia probably reflects changes in diet after diagnosis. Higher prudent-pattern scores were associated with higher intakes of protein, cereal fiber, and magnesium and lower intakes of alcohol, saturated fat, and total fat. Men with higher western-pattern scores generally were younger, had a higher BMI and a lower level of physical activity, were less likely to have hypercholesterolemia, and were more likely to be smokers and of Northern European ancestry. Furthermore, higher western-pattern scores were associated with higher intakes of fat and alcohol and lower intakes of cereal fiber and magnesium. Table 2 also shows the mean intake of foods by quintiles of the dietary pattern scores. Men in the lowest quintile of the western pattern score, for example, had low mean intakes of unprocessed red meat (<3 servings/wk), processed meat (<1 serving/wk), and high-fat dairy products (<5 servings/wk) and high intakes of fish (>4 servings/wk), whole grains (>2 servings/d), vegetables (>4 servings/d), and fruits (>3 servings/d).

During 466 508 person-years of follow-up, we ascertained 1321 cases of type 2 diabetes. As shown in Table 3, the prudent pattern was associated with modestly reduced risk for type 2 diabetes (multivariate relative risk for highest vs. lowest quintiles, 0.84 [95% CI, 0.70 to 1.00]). In contrast, higher western-pattern scores were associated with substantially increased risk for type 2 diabetes (relative risk, 1.59 [CI, 1.32 to 1.93]; $P < 0.001$ for trend). Adjustment for physical activity, cigarette smoking, alcohol consumption, hypercholesterolemia, hypertension, ancestry, and family history of diabetes did not substantially change the associations (Table 3). Results were essentially the same when the analysis was limited to symptomatic type 2 diabetes ($n = 810$).

Table 2. **Baseline Characteristics of the Study Sample, according to Quintile of Energy-Adjusted Dietary-Pattern Score: Health Professionals Follow-up Study, 1986***

Variable	Prudent Dietary Pattern			Western Dietary Pattern		
	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Age, *y*	51.5	53.7	55.0	55.1	53.4	52.2
Ancestry, %						
Northern European	72.2	69.4	66.9	67.3	68.7	73.4
Southern European	22.3	24.3	25.7	24.5	24.1	22.1
Other	4.4	5.0	5.5	6.4	5.5	3.6
Body mass index, *kg/m²*	25.6	25.5	25.2	24.7	25.6	26.0
Physical activity, *METs/wk*†	15.1	20.5	27.9	29.2	19.4	15.1
Current smoking, %	17.3	8.3	5.2	3.2	8.0	18.4
Family history of diabetes, %	18.5	19.7	21.0	19.1	20.4	19.2
Hypertension, %	18.3	19.3	20.2	18.6	19.7	19.0
Hypercholesterolemia, %	7.7	10.2	12.8	13.6	9.9	7.4
Dietary intake						
Alcohol, *g/d*	15.0	10.8	9.7	9.6	11.7	13.2
Protein, *% of energy intake*	16.8	18.7	19.9	19.4	18.5	17.5
Total fat, *% of energy intake*	35.2	32.4	28.2	26.4	32.1	37.2
Saturated fat, *% of energy intake*	12.8	11.1	9.0	8.5	11.0	13.3
Linoleic acid, *% of energy intake*	4.9	5.2	5.1	4.7	5.1	5.5
Cereal fiber, *g/d*	4.7	6.0	6.8	7.7	5.7	4.4
Magnesium, *mg/d*	300	349	420	418	345	307
Food consumption, *servings/d*						
Vegetables	1.8	2.9	5.8	4.4	3.0	2.8
Fruit	1.1	1.7	3.0	3.2	1.6	1.2
Whole grains	0.9	1.4	2.0	2.4	1.2	0.9
Refined grains	1.6	1.1	1.1	1.0	1.1	1.8
Fish	0.2	0.4	0.6	0.6	0.4	0.3
Poultry	0.2	0.3	0.5	0.5	0.3	0.3
Red meat	0.9	0.6	0.4	0.4	0.6	0.9
Processed meat	0.6	0.3	0.2	0.1	0.3	0.7
High-fat dairy products	1.4	0.9	0.8	0.7	0.9	1.5
Sweets and desserts	1.7	1.0	0.8	0.9	1.1	1.4

* Scores are standardized to the age distribution of the total study sample (except for age); quintiles are based on dietary pattern scores adjusted for total energy intake by using the residual method; quintile 1 is the lowest quintile, quintile 3 is the medium quintile, and quintile 5 is the highest quintile. MET = metabolic equivalent hour.

† One metabolic equivalent represents the energy expended at rest.

Table 3. **Relative Risk for Type 2 Diabetes Mellitus, according to Quintile of Dietary Pattern Scores: Health Professionals Follow-up Study, 1986–1998***

Variable	Quintile					*P* Value for Trend
	1 (Lowest)	2	3	4	5 (Highest)	
Prudent pattern score						
Cases of type 2 diabetes, *n/person-years*	291/93 180	229/93 359	286/93 326	263/93 342	252/93 302	
Age- and BMI-adjusted relative risk†	1	0.76	0.94	0.88	0.84	>0.2
Multivariate relative risk (95% CI)‡	1	0.77 (0.65–0.92)	0.96 (0.81–1.14)	0.89 (0.75–1.06)	0.84 (0.70–1.00)	0.2
Western pattern score						
Cases of type 2 diabetes, *n/person-years*	177/93 341	231/93 320	274/93 330	278/93 323	361/93 195	
Age- and BMI-adjusted relative risk†	1	1.18	1.29	1.26	1.54	<0.001
Multivariate relative risk (95% CI)‡	1	1.22 (1.00–1.48)	1.34 (1.10–1.63)	1.34 (1.10–1.63)	1.59 (1.32–1.93)	<0.001

* BMI = body mass index.

† Models were adjusted for age (5-year categories), body mass index (<23.0, 23.0–23.9, 24.0–24.9, 25.0–26.9, 27.0–28.9, 29.0–30.9, 31.0–32.9, 33.0–34.9, or ≥35 kg/m^2), total energy intake (quintiles), and time period (6 periods).

‡ Also adjusted for physical activity (quintiles of metabolic equivalents), cigarette smoking (never, past, or current smoking of 1–14, 15–24, or ≥25 cigarettes/d), alcohol consumption (0, 0.1–4, 5–14, 15–29, or ≥30 g/d), ancestry (Northern European, Southern European, or other), hypercholesterolemia (yes or no), hypertension (yes or no), and family history of type 2 diabetes mellitus (yes or no).

We also examined whether consumption of specific foods with large contributions to the dietary-pattern scores was associated with the risk for type 2 diabetes. Of the foods that characterized the prudent pattern, whole grains had the strongest inverse association with the risk for type 2 diabetes (multivariate relative risk for extreme quintiles, 0.77 [CI, 0.64 to 0.93]; $P = 0.001$ for trend). Consumption of fruit, vegetables, and fish was not appreciably associated with the risk for type 2 diabetes. The foods with major contributions to the western pattern were all positively associated with the risk for type 2 diabetes. (The relative risks for extreme quintiles were: for unprocessed red meat, 1.27 [CI, 1.04 to 1.55]; for processed meat, 1.48 [CI, 1.23 to 1.77]; for refined grains, 1.37 [CI, 1.13 to 1.66]; and for high-fat dairy products, 1.17 [CI, 0.97 to 1.41].) When these western-pattern–associated foods were modeled simultaneously, consumption of processed meat and refined grains remained significantly associated with the risk for type 2 diabetes (relative risk for consumption of processed meat, 1.38 [CI, 1.14 to 1.68]; $P < 0.001$ for trend; relative risk for consumption of refined grains, 1.32 [CI, 1.09 to 1.60]; $P = 0.04$ for trend).

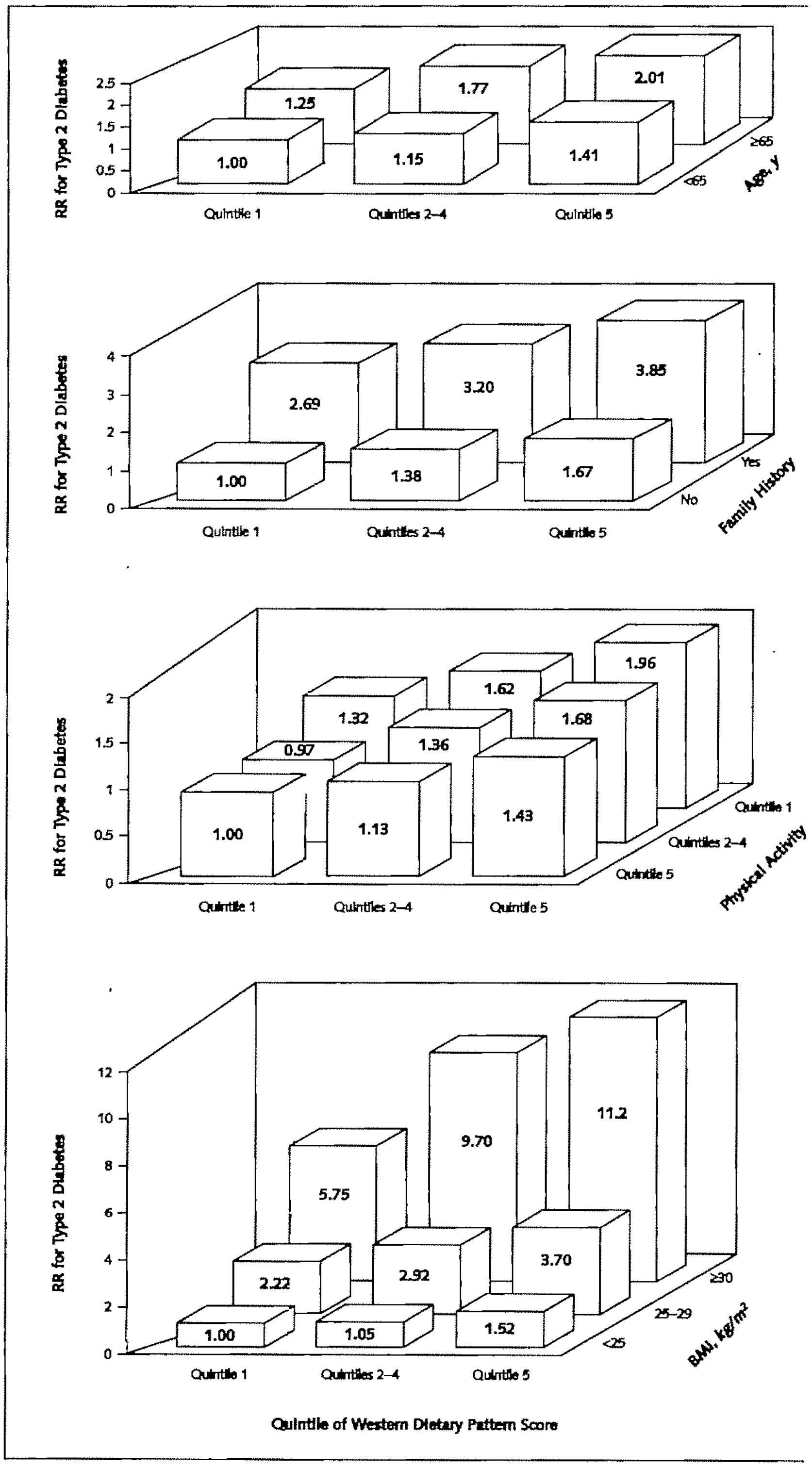
The western dietary pattern was consistently associated with type 2 diabetes in subgroups divided according to age, family history of diabetes, BMI, and physical activity (**Figure**). The combination of a high Western-pattern score with low physical activity was associated with a relative risk (for comparison of combinations of extreme quintiles) of 1.96 (CI, 1.35 to 2.84). We found that the risk for type 2 diabetes was highest for obese men (BMI ≥ 30 kg/m^2) in the highest quintile of the western dietary-pattern scores (relative risk compared with BMI < 25 kg/m^2 and lowest quintile of western pattern score, 11.2 [CI, 8.07 to 15.6]).

DISCUSSION

In this large prospective study of U.S. professional men, we identified two major dietary patterns—a *prudent pattern,* characterized by a high consumption of vegetables, fruits, fish, poultry, and whole grains and a *western pattern,* characterized by a high consumption of red meat, processed meat, high-fat dairy products, French fries, refined grains, and sweets and desserts. The prudent diet was associated with a modestly lower risk for type 2 diabetes. The western pattern, however, was associated with a substantially higher risk for type 2 diabetes. This association was stronger than that for individual foods and was independent of BMI, physical activity, family history of diabetes, and age. The combination of a western dietary pattern with a low level of physical activity or obesity was associated with a particularly high risk for type 2 diabetes.

Two cross-sectional studies examined the association between dietary patterns and type 2 diabetes. In the first, which studied Native Canadians, a "junk food" pattern was associated with a higher prevalence of impaired glucose tolerance and type 2 diabetes (14). In the second, which evaluated a British population, a dietary pattern characterized by high consumption of fruit and vegetables and low consumption of processed meat and fried foods was inversely associated with previously un-

Figure. **Relative risk (*RR*) for type 2 diabetes mellitus, according to combinations of the western dietary pattern score and other risk factors.**



Data are from the Health Professionals Follow-up Study, 1986–1998. Relative risks were multivariate adjusted for the variables listed in the text below Table 3, except the stratifying variable. BMI = body mass index.

diagnosed type 2 diabetes (11). These studies were limited by lack of control for physical activity, which tends to be associated with dietary patterns (8, 11). In one study that had results consistent with our findings, a traditional Pima Indian diet improved glucose tolerance compared with a modern western diet in a short-term dietary intervention (25). Moreover, in a previous subsample analysis of the Health Professionals Follow-up Study, the western dietary pattern was positively associated with fasting plasma insulin level and C-peptide level (26).

In some studies, saturated and total fat intake have been associated with hyperinsulinemia, hyperglycemia, or type 2 diabetes, but the results have not been consistent (7). In our study, saturated and total fat were not appreciably associated with the risk for type 2 diabetes (27). Therefore, the association between the western dietary pattern and type 2 diabetes cannot be explained by saturated or total fat intake. Compared with the contribution of these nutrients, low intake of cereal fiber and magnesium probably contributed more to the increased risk for type 2 diabetes associated with the western pattern (27–29). However, given the magnitude of the association between the western pattern and the risk for type 2 diabetes, it seems unlikely that a single dietary factor was responsible for the observed association.

The prospective design and high rate of follow-up of our study minimize the possibility of recall bias or bias due to loss of follow-up. Diet was inevitably measured with error, and this undoubtedly resulted in some misclassifications. As diet was assessed before type 2 diabetes developed, such misclassification should be nondifferential between cases and noncases and would tend toward underestimation of the true effect. We confirmed self-reported diabetes by a supplementary questionnaire. Validation of assessment of type 2 diabetes with medical records indicated that diabetes reporting was accurate in this medically knowledgeable population. Because screening for blood glucose level was not feasible in this large cohort, underdiagnosis of diabetes is likely. However, compared with the general population, the degree of underdiagnosis was probably smaller in these health professionals with ready access to medical care. Moreover, underascertainment of type 2 diabetes, if not associated with exposure, would not be expected to affect relative risk estimates (30). We also considered the possibility that diet was associated with the likelihood to be screened for diabetes. However, when we restricted the analyses to symptomatic cases, the findings were similar, arguing against presence of surveillance bias.

Principal component analysis requires several arbitrary decisions on the selection of included variables, the number of retained factors, the method of rotation, and the labels of the factors (31). We did multiple sensitivity analyses to examine whether these choices affected the reproducibility of our findings (10). We identified a similar prudent and western pattern by randomly dividing the sample in two groups, including in our analysis all individual food items on the questionnaire (instead of the 37 food groups), retaining three instead of two factors, using the maximum likelihood method instead of the principal component method, and using an oblique (resulting in correlated factors) instead of orthogonal rotation (10). Furthermore, our analysis showed that the reproducibility of the dietary pattern scores over 4-year and 8-year periods is high compared with the long-term reproducibility reported for nutrients (15). Finally, other large U.S. studies (8, 32), which have included women and socioeconomically diverse participants (8), also have identified a prudent and a western pattern that were largely characterized by the same foods. Yet, the association in our study between dietary patterns and the risk for type 2 diabetes needs to be confirmed for women and various ethnic groups.

In conclusion, our findings indicate that major dietary patterns identified by factor analysis can predict risk for type 2 diabetes. Obesity is known to be a strong risk factor for type 2 diabetes (33). However, in addition to balancing total energy intake with expenditure to prevent weight gain, avoiding a western dietary pattern may substantially reduce risk for type 2 diabetes in men.

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Delayed-Onset Heparin-Induced Thrombocytopenia

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Background: **Heparin-induced thrombocytopenia presents 5 to 12 days after heparin exposure, with or without arterial or venous thromboemboli. Delayed recognition and treatment of heparin-induced thrombocytopenia contribute to poor patient outcomes.**

Objective: **To describe and increase awareness of a clinical scenario in which the onset or manifestations of heparin-induced thrombocytopenia are delayed.**

Design: **Retrospective case series.**

Setting: **Three large urban hospitals (with active cardiovascular surgery programs).**

Patients: **14 patients seen over a 3-year period in whom heparin-induced thrombocytopenia became apparent on delayed presentation with thromboembolic complications.**

Measurements: **Platelet counts, onset of objectively determined thromboembolism, results of heparin-induced platelet factor 4 antibody tests, and outcomes.**

Results: **Patients went home after hospitalizations that had included heparin exposure—in most cases, with no thrombocytopenia recognized—only to return to the hospital (median, day 14) with thromboembolic complications. Thromboemboli were venous (12 patients, 7 with pulmonary emboli) or arterial (4 patients) or both. Platelet counts were mildly decreased in all but 2 patients on second presentation. On readmission, 11 patients received therapeutic heparin, which worsened the patients' clinical condition and, in all 11 cases, decreased the platelet count (mean at readmission, 143 × 10^9 cells/L; mean nadir after heparin re-exposure, 39 × 10^9 cells/L). Results of serologic tests for heparin-induced antibodies were positive in all patients. Subsequent treatments included alternative anticoagulants (11 patients), thrombolytic drugs (3 patients), inferior vena cava filters (3 patients) and, eventually, warfarin (11 patients). Three patients died.**

Conclusions: **Delayed-onset heparin-induced thrombocytopenia is increasingly being recognized. To avoid disastrous outcomes, physicians must consider heparin-induced thrombocytopenia whenever a recently hospitalized patient returns with thromboembolism; therapy with alternative anticoagulants, not heparin, should be initiated.**

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Heparin-induced thrombocytopenia is often clinically catastrophic because of attendant venous or arterial thromboembolic complications. Thrombocytopenia is usually recognized 5 to 12 days after initiation of heparin therapy (1). Heparin use is ubiquitous; heparin-induced thrombocytopenia occurs in 3% of patients who receive therapeutic intravenous unfractionated heparin and in 0.5% to 1% of patients who receive lower doses (subcutaneous or flushes), low-molecular-weight heparins, or even the tiny amounts that leach from heparin-coated catheters (2–4).

Lack of awareness and delayed diagnoses have contributed to the substantial morbidity and mortality in patients with heparin-induced thrombocytopenia. The impact of missed diagnoses has increased with the availability of more effective therapeutic strategies (5, 6). We highlight a repetitive clinical scenario in which recently hospitalized patients with heparin exposure return to the hospital after several days to a few weeks with thrombotic complications—a phenomenon we call *delayed-onset heparin-induced thrombocytopenia*. Even in medical centers familiar with heparin-induced thrombocytopenia, at first physicians rarely consider the possible relationship between the thromboembolism and previous heparin exposure.

METHODS

We collected data on 14 patients who met our criteria for delayed-onset heparin-induced thrombocytopenia. From 1997 to 2000, these 14 patients were seen at the Methodist Hospital or St. Luke's Episcopal Hospital in Houston, Texas, or at the Hemostasis and Thrombosis Center of Florida Hospital in Orlando, Florida; during that period, an estimated 260 additional patients with heparin-induced thrombocytopenia were also seen at these institutions. Our criteria for delayed-onset heparin-induced thrombocytopenia were exposure to heparin; discharge after a reasonably benign hospital course, during which heparin-induced thrombocytopenia went unrecognized; representation with objectively proven venous or arterial thromboembolism; and thrombocytopenia at an appropriate time after heparin exposure or reexposure. (The course of 1 patient, patient 3, varied slightly from the others in that heparin-induced thrombocytopenia was suspected during initial hospitalization. We include this case because the serial platelet counts clearly demonstrate a delayed-onset component.) All patients had serologic tests for heparin-induced platelet factor 4 antibodies by enzyme-linked immunosorbent assay (ELISA; GTI, Brookfield, Wisconsin) (11 patients) or by platelet aggregometry in citrated plasma (3 patients) (7). Unless otherwise stated, the day of event and day 1 refer to the day of first heparin exposure.

Case Reports

Patient 1

A 75-year-old man (**Figure**, *top*) had an infected knee prosthesis removed. From postoperative day 1 until discharge on postoperative day 9, he received enoxaparin, 30 mg subcutaneously twice daily. Three days after discharge, he was readmitted for a swollen, dusky left arm, the site of a subclavian catheter. Venography showed subclavian thrombosis. The platelet count was 145 × 10^9 cells/L. The patient began receiving enoxaparin, 80 mg subcutaneously twice daily. The platelet count decreased to 85 × 10^9 cells/L the morning after reinitiation of enoxaparin therapy. His arm markedly worsened with impending gangrene. At the recommendation of a hematology consultant on day 15, the patient received tissue plasminogen activator followed by hirudin therapy. The arm improved dramatically within 2 days, and the platelet count increased to 148 × 10^9 cells/L. The result of ELISA for heparin-induced antibodies was positive. At discharge, the patient was taking warfarin and had fully recovered, with a platelet count of 240 × 10^9 cells/L.

Patient 2

A 60-year-old woman underwent repair of an aortic aneurysm with aortic valve replacement. She received enoxaparin, 30 mg subcutaneously twice daily from postoperative days 1 through 6. On day 4, she experienced transient amnesia that was attributed to medications. She was taking warfarin at discharge. The patient was readmitted 33 days after initial heparin exposure (postoperative day 30) with proximal-thigh deep venous thrombosis despite a prothrombin international normalized ratio of 4.2. Thrombosis was confirmed by Doppler ultrasonography. Immediately after receiving an intravenous heparin bolus, she developed dyspnea, tachycardia, and hypotension, which required intubation and mechanical ventilation. An inferior vena cava filter was placed for suspected pulmonary embolus. The platelet count was 420 × 10^9 cells/L on readmission but then decreased hours later (after she received the heparin bolus) to 47 × 10^9 cells/L. A ventilation–perfusion scan was normal. The patient tested positive on ELISA for heparin antibody. After beginning danaparoid therapy, the patient improved rapidly and was discharged with a platelet count of 343 × 10^9 cells/L.

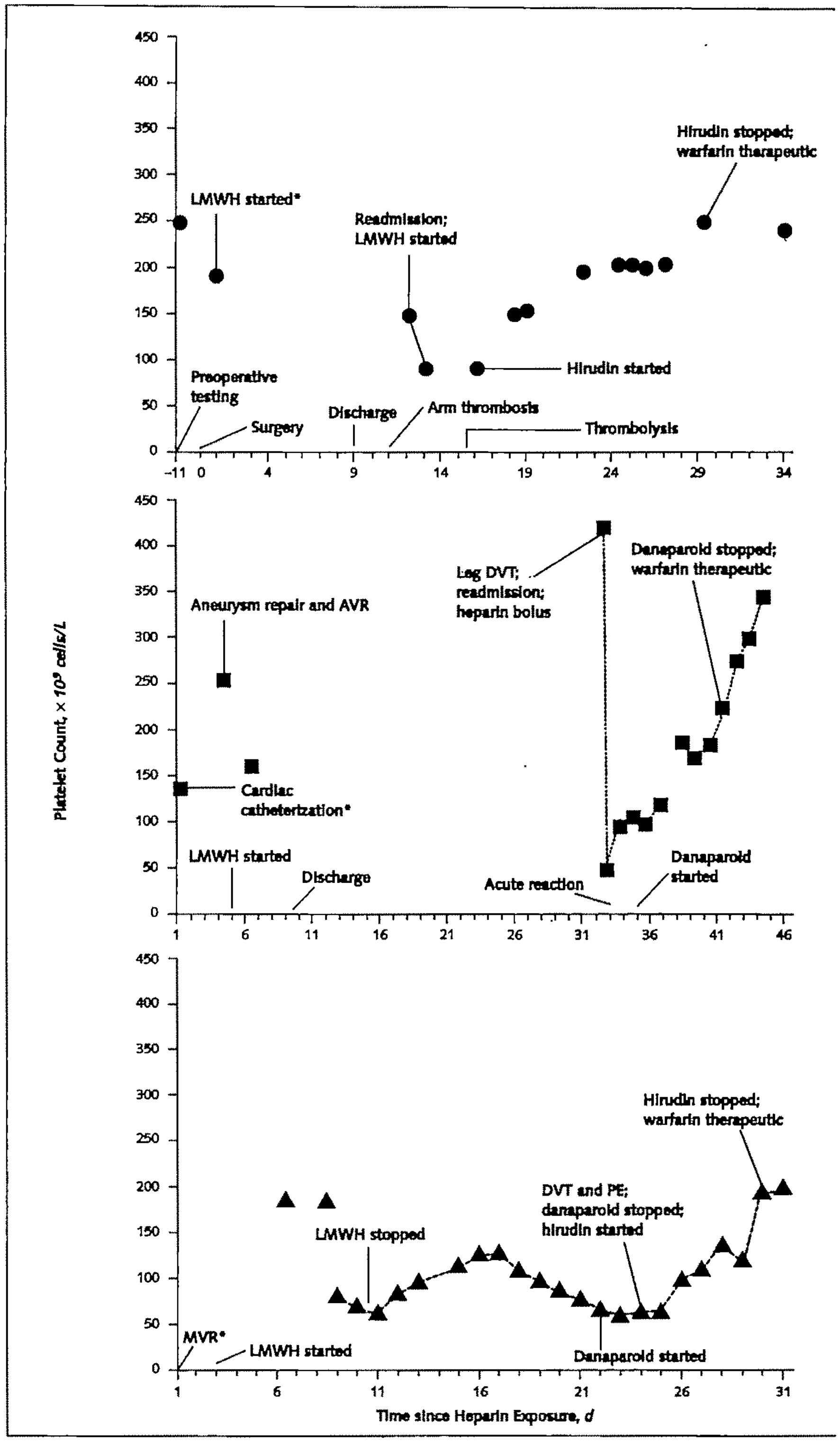
Patient 3

A 78-year-old woman underwent mitral valve repair. She was slow to ambulate independently. Therapy with enoxaparin, 30 mg subcutaneously, was initiated on day 2 but was stopped on day 10, when the platelet count was 78 × 10^9 cells/L. The platelet count increased until day 19, when it began to decline again. Hospital discharge had been planned for day 22 but was canceled because the platelet count was 60 × 10^9 cells/L. The fibrin split product level was 40 mg/L (normal ≤ 10 mg/L), the D-dimer level was 4.0 mg/L (4.0 μg/mL) (normal ≤ 0.5 mg/L [≤0.5 μg/mL]), and the fibrinogen level was 2.23 μmol/L (normal, 4.41 to 11.76 μmol/L). The result of a platelet aggregation test for heparin antibodies was positive. Investigation revealed no explanation other than heparin-induced thrombocytopenia for the patient's disseminated intravascular coagulation. For the first 2 days of danaparoid therapy, the platelet count and coagulation values did not improve. The patient developed pain and swelling of the thigh, dyspnea, pleuritic pain, and hemoptysis. Ventilation–perfusion scanning demonstrated pulmonary emboli, and Doppler ultrasonography showed proximal deep venous thrombosis with caval extension. Laboratory values and clinical abnormalities improved dramatically with lepirudin therapy. (Results on a serotonin release assay for heparin antibody were "equivocal" in a reference laboratory, and danaparoid cross-reactivity was similarly equivocal.) The patient began treatment with warfarin; she recovered and was discharged.

RESULTS

Twelve of the 14 patients were exposed to unfractionated heparin as a result of cardiovascular surgery (**Table**). Four of these 12 patients were later exposed to

Figure. **Three cases of delayed-onset heparin-induced thrombocytopenia.**



Shown are the platelet counts and clinical courses of patient 1 (*top*), patient 2 (*middle*), and patient 3 (*bottom*). *First day of heparin exposure. AVR = aortic valve repair; DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; MVR = mitral valve replacement; PE = pulmonary embolism.

Table. **Features of 14 Cases of Delayed-Onset Heparin-Induced Thrombocytopenia***

Patient	Indication for Heparin	Return Diagnosis	Day of Complication†	Platelet Count on Re-presentation, × 10^9 cells/L	Platelet Count after Re-exposure, × 10^9 cells/L	Outcome (Day of Discharge)†
1	Knee surgery	DVT in arm	11	145	85	Recovered (34)
2	Aortic valve repair and aneurysm repair	DVT	33	420	47	Recovered (44)
3	Mitral valve repair	DVT and PE	24	130‡	–§	Recovered (31)
4	Aortic valve repair	PE; ischemic cerebrovascular accident	10	251	42	Died (18)
5	Unstable angina and CABG	DVT and PE	12	66	19	Recovered (25)
6	Central line flush (osteomyelitis)	DVT in arm and PE	9	109	17	Recovered (43)
7	CABG	Inferior vena cava and renal vein thromboses; myocardial infarction	16	84	27	Died (41)
8	CABG	DVT and PE	11	–‖	76	Recovered (22)
9	CABG	Arterial thrombosis in arm	40	75	6	Died (47)
10	CABG	DVT and PE	12	87	31	Recovered (16)
11	PTCA and CABG	Arterial thrombosis in leg	14	70	32	Recovered (23)
12	CABG	DVT	18	84	–§	Recovered (37)
13	CABG	DVT	19	87	–§	Recovered (26)
14	CABG	DVT and PE	14	123	87	Recovered (23)

* CABG = coronary artery bypass grafting; DVT = deep venous thrombosis; PE = pulmonary embolism; PTCA = percutaneous transluminal coronary angioplasty.
† The first day of heparin exposure is considered day 1.
‡ Patient 3 had not been discharged initially from the initial hospitalization.
§ Patient was not re-exposed to heparin.
‖ Platelet count was not checked.

low-molecular-weight heparin. One patient was exposed only to catheter flushes with unfractionated heparin during the initial hospitalization, and only patient 1 was exposed exclusively to low-molecular-weight heparin. Before first hospital discharge, platelet counts were not checked for several days in 8 patients. In 3 patients, the platelet counts were normal before the first discharge (170 × 10^9 cells/L on day 7, 211 × 10^9 cells/L on day 8, 317 × 10^9 cells/L on day 10). Three other patients did have low platelet counts (range, 56 to 124 × 10^9 cells/L) during the first hospitalization, but among these patients, heparin-induced thrombocytopenia was suspected only in patient 3; another patient was receiving corticosteroids for misdiagnosed immune thrombocytopenia at discharge; and in the third patient, a low platelet count was ignored.

Thrombotic complications were recognized a median of 13 days after initial heparin exposure (range, 9 to 40 days) and included venous thromboembolism in 12 patients (7 with pulmonary emboli) and arterial thrombosis in 4 patients (2 patients had both). At return presentation with thrombosis, 11 patients had mild to moderate thrombocytopenia (median platelet count at readmission, 87 × 10^9 cells/L) and only 2 patients had a normal platelet count. (In 1 patient, the physicians reinstituted heparin therapy without first establishing the platelet count, which had not been measured since the previous discharge.) Eleven patients were re-exposed to therapeutic heparin. This precipitated a decrease in the platelet count in less than 24 hours in all re-exposed patients (mean platelet count at readmission, 143 × 10^9 cells/L; mean after re-exposure, 39 × 10^9 cells/L [range, 6 to 87 × 10^9 cells/L]), and many of these patients experienced obvious clinical worsening. After heparin-induced thrombocytopenia was recognized, 11 patients received alternative anticoagulants (lepirudin [8 patients], danaparoid [3 patients], or argatroban [2 patients]). Other treatments included tissue plasminogen activator (3 patients), inferior vena cava filters (3 patients), surgical embolectomy (1 patient) and, eventually, warfarin (11 patients). The median duration of the second hospitalization was 9 days. Three patients died. A serologic test for heparin-induced antibodies had positive results in all 14 patients.

DISCUSSION

We describe a recurrent clinical scenario in which patients exposed to heparin are discharged after an apparently benign hospital course, only to return with thromboembolism in a few days to a few weeks (median, day 14 [range, 9 to 40 days]). As is seen in typical heparin-induced thrombocytopenia, the patients had venous thromboembolism (10 patients), arterial thromboembolism (2 patients), or both (2 patients). In most cases, thrombocytopenia went unrecognized during the first hospitalization; in 3 patients, the platelet count had been normal just before discharge, and in 8 patients, the platelet count had not been checked. Three patients did have a low platelet count 7 to 10 days into their first hospital course, but unfortunately, this did not trigger interventions for heparin-induced thrombocytopenia that might have avoided later complications. Another valuable clue to underlying heparin-induced thrombocytopenia might have been the mild to moderate thrombocytopenia present in all but 2 patients at re-presentation with thrombosis. Nevertheless, the relationship of the thromboembolism to previous heparin exposure was rarely considered; thus, 11 patients were treated with therapeutic unfractionated heparin or low-molecular-weight heparin. The use of heparin precipitated a prompt decrease in the platelet count, often with overt clinical deterioration. This is epitomized in patient 2, who had an immediate reaction after re-exposure that was characterized by hypotension and dyspnea; such a reaction in patients with heparin-induced thrombocytopenia has been previously described (8). In retrospect, we believe that the transient amnesia experienced during this patient's first hospitalization also was related to the heparin-induced thrombocytopenia (9). The thromboembolic complications proved fatal in 3 of the patients.

We believe that this syndrome is best described as "delayed-onset" heparin-induced thrombocytopenia, although in some patients, "delayed-manifest" or "delayed-recognized" might be technically more accurate. In at least three patients, the platelet count had decreased 5 to 12 days after the start of heparin exposure, as is consistent with classic heparin-induced thrombocytopenia. The courses of these three patients exemplify and corroborate reports of thromboembolic complications that subsequently arise in patients with isolated heparin-induced thrombocytopenia—that is, patients without thrombosis on initial diagnosis—who do not receive alternative anticoagulation (10, 11). The incidence of subsequent thromboembolism in such patients is reported to be very high (10, 11). Some of the eight patients with unchecked platelet counts would probably also exemplify this phenomenon; however, the lack of platelet data precludes validating a diagnosis of heparin-induced thrombocytopenia during initial hospitalization. On the other hand, onset of thrombocytopenia truly was delayed in the patients with a normal platelet count before initial discharge and in patient 3, whose platelet count had decreased for a second time in the absence of renewed heparin exposure. The pathophysiologic cause may involve increasing antibody titer, cross-reactivities between the heparin-induced antibodies and endogenous glycosaminoglycans and platelet factor 4, and momentum generated by a burgeoning consumptive coagulopathy.

Cognizance of delayed-onset heparin-induced thrombocytopenia becomes more important as effective therapeutic strategies are honed. Promptly removing all sources of heparin exposure can favorably affect patient morbidity and mortality. Withdrawing the heparin therapy (or source) is insufficient by itself; in addition, alternative anticoagulants are indicated because patients at that stage face an ongoing serious risk for thrombosis (10–12). Early use of warfarin should be avoided in patients with heparin-induced thrombocytopenia (13). Alternative anticoagulants with recorded success in heparin-induced thrombocytopenia include lepirudin, argatroban, and danaparoid (14–16). The case of patient 3 raises the possibility of clinically infrequent crossreactivity between danaparoid and heparin-induced antibodies. Judicious use of thrombolytic therapy and surgical interventions are beneficial in select cases.

Physician education is essential to preventing delayed-onset heparin-induced thrombocytopenia and to improving clinical outcomes. Given the frequency and seriousness of heparin-induced thrombocytopenia, the current underemphasis of this condition in medical textbooks and educational curricula is puzzling. Scenarios of the delayed-onset type are being recognized with increasing frequency at our medical centers. Pressures likely to make this increasingly common include earlier hospital discharges, "clinical pathways" that limit laboratory testing, and trends toward outpatient heparin therapy. Patients with significant heparin exposure should have platelet counts monitored every other day, beginning on day 4 (17). Delayed-onset heparin-induced thrombocytopenia should be a primary diagnostic consideration whenever a recently hospitalized patient presents with thromboembolism. Physicians should be aware that even a modestly low platelet count on representation could be an essential clue to underlying heparin-induced thrombocytopenia. In such cases, physicians could initiate early alternative anticoagulant therapy, instead of heparin therapy, to interrupt the thrombotic diathesis.

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Chiropractic: A Profession at the Crossroads of Mainstream and Alternative Medicine

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Chiropractic is a large and well-established health care profession in the United States. In this overview, we briefly examine the development of chiropractic from humble and contentious beginnings to its current state at the crossroads of alternative and mainstream medicine. Chiropractic has taken on many of the attributes of an established profession, improving its educational and licensing systems and substantially increasing its market share in the past two decades. The public increasingly uses chiropractic largely for spinal pain syndromes and appears to be highly satisfied with the results. Of all the so-called alternative professions, chiropractic has made the largest inroads into private and public health care financing systems and is increasingly viewed as an effective specialty by many in the medical profession. Much of the positive evolution of chiropractic can be ascribed to a quarter century–long research effort focused on the core chiropractic procedure of spinal manipulation. This effort has helped bring spinal manipulation out of the investigational category to become one of the most studied forms of conservative treatment for spinal pain. Chiropractic theory is still controversial, but recent expansion in federal support of chiropractic research bodes well for further scientific development. The medical establishment has not yet fully accepted chiropractic as a mainstream form of care. The next decade should determine whether chiropractic maintains the trappings of an alternative health care profession or becomes fully integrated into all health care systems.

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Chiropractic is the largest, most regulated, and best recognized of the professions that have traditionally functioned outside of mainstream medical institutions and, in the new lexicon, have fallen into the category of "complementary and alternative medicine." It is unique in the United States as the most widely disseminated indigenous U.S. system of healing. Its steadily increasing acceptance and use by the public and payers indicate that chiropractic is no longer the "marginal" or "deviant" profession it was once considered to be (1). According to surveys of patients seeking alternative care, chiropractors are used more often than any other alternative provider group (2), and the satisfaction with chiropractic care is very high (3, 4). The number of chiropractors is growing: The current number of 60 000 is expected to reach 100 000 by 2010 (5).

Although some observers suggest that the profession may be entering the health care mainstream (6, 7), chiropractic remains a young profession; in 1995, it celebrated its 100th anniversary. Until the mid-1970s, chiropractic was considered to be outside mainstream medicine, often an outcast, and most chiropractors viewed themselves as differing in philosophy and practice from other health care practitioners (8). During the past two decades, there has been a marked change in the manner in which chiropractic is viewed, not only by mainstream medical practitioners (9) and institutions (10, 11) but also by members of the profession itself (12). Examining the factors that led to this change in attitude and the legitimization of chiropractic as a method of treatment and as a profession, as well as the conflicting emotional discussion that has accompanied these changes, is an interesting and informative exercise in health care sociology (13). The changes in the chiropractic (and medical) profession are, however, still in the transitional phase, and the acceptance and even the future role of chiropractic in the overall health care system remain controversial (14, 15).

THE ORIGINS AND HISTORY OF CHIROPRACTIC

Chiropractors have designated 18 September 1895, when Daniel David Palmer reportedly gave his first spinal adjustment, as the origin of the chiropractic profession; however, spinal manipulation is one of the oldest and most widely practiced healing methods. References to spinal manipulation, and even the term *subluxation*, can be traced back as far as Hippocrates and Galen (16), and manual and manipulative procedures have been depicted in the art and writings of most ancient cultures. Although manipulation has been part of orthopedic medical practice for centuries, most nonmedical practitioners of spinal manipulation in the 19th century were

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"bonesetters" who had learned their skills primarily by apprenticeship and observation (17).

The early and middle years of chiropractic were dominated by charismatic and authoritarian figures who often disagreed with one another. Many of the early schisms around the theory and scope of practice from this period still exist in some form (9, 17). Daniel David Palmer, who originally practiced as a lay magnetic healer, is credited with professionalizing the practice of spinal manipulation. He integrated popular natural health and scientific models of the day to present a unique theory of chiropractic. He did this by incorporating the concept of an inherent healing ability of the body, which he named "innate intelligence," into concepts drawn from contemporary knowledge about anatomy and physiology. He eschewed the use of drugs and surgery as unnatural invasions to the body and focused on what he perceived as normalizing the function of the nervous system as the key to health (17).

From the beginning, chiropractors understood that professional self-regulation and independent legal status were crucial to survival. This stormy history of the first century of chiropractic includes many milestones on the march to professionalization, some of which are listed in Table 1. Although chiropractic originated in the United States (the primary training ground and theoretical inspirational source for chiropractors), it took less than 10 years for chiropractors to immigrate and begin practice in other countries. In 1923, the province of Alberta in Canada became the first jurisdiction to license chiropractic outside of the United States; in 1939, the canton of Zürich in Switzerland was the first to license the profession outside of North America. Today, chiropractors are licensed and regulated in many countries throughout the world (18) and are permitted to practice in most countries, pursuant to general law.

CHIROPRACTIC IN HEALTH CARE

One indicator of chiropractic mainstreaming is the steadily increasing use by patients in the United States, which has tripled in the past two decades from about 3.6% according to a 1980 survey (19) to an estimated 11% according to a 1997 national random telephone survey (2). This translates to an estimated 190 million patient visits to chiropractors in a year, or about 30% of visits to all complementary and alternative practitioners (2). One recent survey of family physicians and chiropractors in North Carolina (20) found that two thirds of the medical physicians felt "moderately" or "very" informed about chiropractic. Furthermore, 65% admitted referring patients to chiropractors, and 98% of chiropractors made routine referrals to physicians.

Table 1. **Events in the Historical Development of Chiropractic**

Year	Historical Milestones
1905	Minnesota is the first state to license chiropractic as an independent profession.
1922	California recognizes and licenses chiropractors.
1933	The U.S. Council of State Chiropractic Examiners is established with a mandate to provide unified standards for licensure. It is now the Federation of Chiropractic Licensing Boards.
1944	The Foundation for Chiropractic Education and Research is established and remains the profession's foremost agency for funding postgraduate training and research.
1963	The National Board of Chiropractic Examiners is established to create standardized examinations and promote consistency and reciprocity between state examining boards.
1974	Louisiana is the last state to grant licensure to chiropractors.
1974	The U.S. Council on Chiropractic Education is recognized by the U.S. Department of Education as the sole accrediting agency for schools of chiropractic.
1975	The U.S. National Institute of Neurological Diseases and Stroke convenes a multidisciplinary conference to examine the research status of "spinal manipulative therapy."
1976	*Journal of Manipulative and Physiological Therapeutics* is founded as a scientific peer-reviewed chiropractic journal and is indexed by the National Library of Medicine.
1987	The U.S. Supreme Court upholds a lower-court decision that finds the American Medical Association guilty of antitrust violations in its attempt to eliminate the chiropractic profession.
1994	The U.S. Agency for Health Care Policy and Research convenes an evidence-based consensus panel that rates spinal manipulation as an effective treatment for back pain.
1997	The Consortial Center for Chiropractic Research is established by a grant from the U.S. National Institutes of Health.

Payments for chiropractic care historically came directly from patients' pockets until chiropractic services were included in Medicare in the 1970s. In the past few decades, chiropractic has been included in a substantial proportion of private and public insurance plans, all state workers-compensation systems, and all forms of managed care (including health maintenance organizations). More than 50% of health maintenance organizations and more than 75% of private health insurance plans now offer chiropractic services (21). Under order of the U.S. Congress, the military health care system has initiated a series of demonstration projects to investigate the feasibility of providing chiropractic care to military personnel.

CHIROPRACTIC TRAINING AND LICENSURE

From many proprietary schools hastily established during the first part of the 20th century, a stable number of chiropractic training institutions have emerged in the United States. Unlike in the United States, where all but one college are privately funded, chiropractic education in Australia, South Africa, Denmark, one college in Canada, and two in Great Britain is provided at established government-sponsored universities and colleges. Most colleges in the United States are accredited by the Council on Chiropractic Education, an agency certified by the U.S. Department of Education. Each college requires at least 4 academic years of professional education before students can qualify for licensure examinations. A minimum of 60 units of prescribed college-level courses (increasing to 90 units by 2002), mostly in the sciences, is required before admission to chiropractic college. Approximately 50% of students enter chiropractic training with a baccalaureate degree.

A recent study described U.S. chiropractic curricula as an average of 4820 classroom and clinical hours, with about 30% spent in the basic sciences and 70% in clinical sciences and internship (22). Medical school curricula average about 4670 hours with a similar breakdown. Compared with medical students, chiropractic students spend more hours in anatomy and physiology but fewer in public health. Both programs have similar hours in biochemistry, microbiology, and pathology. Chiropractic curricula provide relatively little instruction in pharmacology, critical care, and surgery but emphasize biomechanics, musculoskeletal function, and manual treatment methods. Medical education has more than twice as many hours in actual clinical experience but 1000 fewer hours in didactic and workshop-like clinical courses. All chiropractic colleges maintain busy training clinics that deliver chiropractic care in settings similar to typical chiropractic practice. Specialty training is available in 2- to 3-year postgraduate residency programs in radiology, orthopedics, neurology, sports, rehabilitation, and pediatrics. Coursework leads to eligibility for accredited specialty board competency examinations, which confer "diplomate" or "certified" status.

Forty-six states either recognize or require passage of examinations administered by the National Board of Chiropractic Examiners in the areas of basic science, clinical science, and clinical competency before granting a graduate a license to practice. Most states also require annual proof of continuing education credits for ongoing license renewal.

CHIROPRACTIC HEALTH CARE AND PRACTICE CHARACTERISTICS

Chiropractic is an evolving health profession with functions, values, traditions, and training institutions similar to those of other professions. As envisioned by its founder, chiropractic was to be a revolutionary system of healing based on the premise that neurologic dysfunction caused by "impinged" nerves at the spinal level was the cause of most "dis-ease" and that spinal manipulation (adjustment) removed the interference to a full and healthy expression of life. Modern chiropractic theory and practice have moved away from the original monocausal theory, and research is gradually redefining the nature of the discipline and its education. Many still think "chiropractic" is synonymous with "spinal manipulation," but as described below, this is only partially accurate. With the advent of the category "complementary and alternative medicine" (CAM), chiropractors themselves are divided about how to define the profession; many do not want to be termed CAM practitioners (23). Chiropractors have many of the attributes of primary care providers and often describe themselves as such (24). Others point out that chiropractic has more of the attributes of a limited medical profession or specialty, akin to dentistry or podiatry (1). This is an ongoing internal and external debate affected by dynamic health industry forces.

Spinal Manipulation: The Chiropractic Adjustment

The core clinical action that all chiropractors agree upon is spinal manipulation. Chiropractors much prefer the term spinal "adjustment," reflecting their belief in the therapeutic and health-enhancing effect of correcting spinal joint abnormalities. Dozens of adjusting "techniques" exist, and discussions about their relative merits make up much chiropractic academic discourse (25, 26). The procedure in its broadest definition describes application of a load (force) to specific body tissues with therapeutic intent. This load, which has traditionally been delivered by hand, can vary in its velocity, amplitude, duration, and frequency, as well as anatomic location, choice of levers, and direction of force.

Although "spinal manipulation" is traditionally associated with "chiropractic" (chiropractors deliver >90% of the manipulations in the United States [27]), chiropractors also provide many other treatments and counselling services. Physical therapies such as heat, cold, electrical methods, and rehabilitation methods are common (28, 29). Chiropractors usually suggest therapeutic exercises and general fitness recommendations to most patients, and give advice to many patients about nutrition, vitamins, weight loss, smoking cessation, and relaxation techniques (30). Many chiropractors use other forms of CAM, with emphasis on massage, acupressure, and mineral and herb supplements (23).

Chiropractic Case Mix

Studies confirm that most patients go to chiropractors for musculoskeletal problems: about 60% with low-back pain, and the remainder with head, neck, and extremity symptoms (28, 31). Approximately one third of all patients who seek professional care for low-back pain consult chiropractors in a primary health care role (32–34). Furthermore, about half of the patients seeking chiropractic care have chronic symptoms (31, 35). Only a small number, typically fewer than 2% to 5%, seek care for other conditions. Recent studies have also documented that a minor proportion of patients visit chiropractors for general health concerns, prevention, and a feeling of well-being; they often receive standard health advice, most often with regard to physical fitness and nutrition (35–37).

Diagnostic and Assessment Methods

The approach used in chiropractic training and practice for clinical diagnosis is similar to that of all health care disciplines: a history, physical examination, and specialty-specific assessments (25, 38). The Council on Chiropractic Education specifies that these basic clinical competencies must be taught in all accredited institutions, and chiropractors are expected to differentiate mechanical musculoskeletal problems from visceral abnormalities that may present with a similar clinical picture (29). Chiropractic practice guidelines developed by the profession rate history taking, physical examination, and periodic reassessments of progress as "necessary" attributes of good practice (39).

By using job analysis concepts, the National Board of Chiropractic Examiners has provided the most thorough description of chiropractic practice (28). Chiropractors rated "extremely important" the knowledge needed to arrive at a diagnosis on the basis of information gathered from a patient's history and physical, neurologic, and orthopedic examinations. In most states, chiropractors have the statutory right and obligation to render a medical diagnosis, especially within their scope of customary and legal practice. Patients with diagnoses not amenable to chiropractic care are routinely referred (20).

Chiropractors' use of advanced diagnostic tests is generally low, reflecting the typical nature of the musculoskeletal caseload (29). The main exception is plain-film radiography, which has been traditional in chiropractic ever since its development at the beginning of the 20th century. Much training time is spent on the technique and interpretation of musculoskeletal radiographs (22, 40, 41). In regard to radiographic examination, the job analysis survey indicated that chiropractors "frequently" obtain radiographs for new patients to determine abnormality; they "sometimes" obtain radiographs to determine instability or joint dysfunction; they "frequently" determine the possible site and nature of a manipulable subluxation; they "frequently" perform radiography on a patient whose condition is deteriorating or who is not responding to care; and they "rarely" obtain radiographs to monitor a patient's progress. Chiropractors consider knowledge of normal radiographic anatomy and of radiographic interpretation and diagnosis to be "extremely important" (28).

Indications for radiography are hotly debated in chiropractic circles, but use appears to be declining over time (42). The use of radiography may also vary substantially by geographic region. A practice-based study comparing chiropractic and physician practices for patients with back pain in Oregon found that 26% of patients of both provider groups had radiography (43). Carey and colleagues (4) found higher rates of use in North Carolina: 67% for chiropractors and 72% for orthopedists. Of note, since the inception of Medicare 30 years ago, chiropractors had been mandated to obtain radiographs in order to be reimbursed for care. Only after persistent legislative activity has this provision finally been changed (44).

The Chiropractic Clinical Encounter and Patient Perceptions

Chiropractors use the information from the case history and examination to ascertain the patient's state of health and to form a diagnostic impression, with additional studies obtained as needed. Focal joint, muscle, and soft tissue examinations are usually performed to determine the potential utility of spinal manipulation and other interventions. These usually include palpation, assessing the range and quality of joint motion, and probing for tenderness and inflammation. On the basis of the findings, the chiropractor chooses a treatment plan and estimates prognosis. Essentially, patients may receive a trial of chiropractic care, be referred for co-management, or be referred to an appropriate specialist. The profession has developed detailed consensus guidelines for quality for most aspects of case management (39), and these are didactically and clinically modeled in accredited chiropractic institutions.

The clinical encounter tends toward a high-touch, low-technology health model with more concern for the person than the disease. Chiropractors believe in the inherent healing ability of the body and communicate the hope of healing to patients. Spinal manipulation and other forms of touching care require that a level of trust develop between the patient and the chiropractor. Repeated visits allow a relationship to flourish that is often used to communicate on a social and psychological level as well as about biological implications of care (45).

One recent essay opined that much of chiropractic's success and perhaps its most important contribution to health care might concern this patient–physician relationship (7). Analyses from anthropologic and sociologic perspectives have suggested that treatment by a chiropractor, especially for many patients with chronic pain, can generate a sense of understanding and meaning, an experience of comfort, an expectation of change, and a feeling of empowerment (46, 47). The hands-on and compassionate "can do" clinical behavior of the typical chiropractor seems to be concrete, reassuring, and immediately satisfying. Observational studies (3, 4) and randomized trials (48) leave little doubt that chiropractic patients are very satisfied with their management.

CHIROPRACTIC THEORY AND RESEARCH

Throughout the short history of chiropractic, the profession has had the difficult task of justifying a treatment partially rooted in quasi-mystical concepts to a skeptical mainstream medical and scientific community. Confounding this problem has been the fact that pain, especially chronic musculoskeletal pain, remains something of a scientific enigma (49). A 1975 National Institute of Neurological Diseases and Stroke conference, "Research Status of Spinal Manipulative Therapy," pointed out the lack of any substantial research to justify claims made by chiropractors or any other practitioner of manipulation (50); by doing so the conference galvanized a quarter century–long research effort.

Focus of Research

Two broad categories of research have been pursued: 1) clinical outcomes in randomized clinical trials and observational studies and 2) basic science efforts attempting to understand the biological mechanisms of spinal manipulation. For this report, we supplemented our own exhaustive reference collections of randomized clinical trials of spinal manipulation with additional searches of MEDLINE, MANTIS, CHIROLARS, and the Cochrane Collaboration Library. We tracked citations and manually searched relevant journals to verify that the list was as complete as possible. We made no attempt to find finished unpublished clinical trials or review non–English-language reports.

To date, at least 73 randomized clinical trials of a broadly defined spinal manipulation procedure can be found in the English-language literature. Most trials have been published in general medical and orthopedic journals (for example, *British Medical Journal*, *Journal of the American Medical Association*, *Spine*). Nineteen papers were published in the chiropractic peer-reviewed literature (for example, *Journal of Manipulative and Physiological Therapeutics*). Most first authors have medical degrees, and 23 papers were written by chiropractors. Authors did not necessarily publish in the literature of their profession. While publication bias cannot be ruled out, there is no evidence of it in this information.

Most of these studies have been conducted on patients with low-back, neck, and head pain, and a few have examined other conditions. The clinical trials include placebo-controlled comparisons, comparisons with other treatments, and pragmatic comparisons of chiropractic management with common medical management (**Table 2**).

Forty-three randomized trials of spinal manipulation for treatment of acute, subacute, and chronic low-back pain have been published. Thirty favored manipulation over the comparison treatments in at least a subgroup of patients, and the other 13 found no signif-

Table 2. **Results of Randomized, Controlled Trials of Spinal Manipulation**

Condition	Randomized, Controlled Trials, *n*	Results	References
Acute back pain	10	Positive	51–63
	3	Equivocal	
Subacute and chronic back pain	9	Positive	64–79
	6	Equivocal	
Mixed acute and chronic back pain	10	Positive	48, 80–94
	4	Equivocal	
Sciatica	1	Positive	95
Migraine headache	2	Positive	96–98
	1	Equivocal	
Muscle tension headache	4	Positive	99–103
	1	Equivocal	
Cervicogenic headache	1	Positive	104
Acute, subacute, chronic neck pain	4	Positive	72, 73, 91, 92, 105–113
	7	Equivocal	
Elbow pain	1	Positive	114
Dysmenorrhea	1	Positive	115, 116
	1	Equivocal	
Infantile colic	1	Positive	117
Enuresis	1	Equivocal	118
Asthma	2	Equivocal	119, 120
Premenstrual syndrome	1	Positive	121
Carpal tunnel syndrome	1	Equivocal	122
Hypertension	1	Positive	123, 124
	1	Equivocal	

icant differences. No trial to date has found manipulation to be statistically or clinically less effective than the comparison treatment. Eleven of the low-back pain trials included a placebo group; 8 of them showed an advantage to manipulation (125). Eleven randomized, controlled trials of spinal manipulation for neck pain have been conducted; 4 had positive findings and 7 were equivocal. Seven of 9 randomized trials of manipulation for various forms of headache were positive.

In most of the randomized, controlled trials of manipulation for musculoskeletal pain, the positive effect sizes appear to be clinically and statistically significant but not dramatic, leaving room for various interpretations. Systematic reviews and meta-analyses conducted in the early to mid-1990s made cautiously positive or equivocal statements about the effectiveness of manipulation for low-back pain, neck pain, and headache, and called for higher-quality studies (27, 125–129).

Using formal consensus processes, in 1995 the Quebec Task Force on Whiplash-Associated Disorders concluded that spinal manipulation had at least "weak cumulative evidence," and recommended that a short regimen of spinal manipulation may be used as a therapeutic trial for neck pain (130). In 1994, the U.S. Agency for Health Care Policy and Research similarly concluded that spinal manipulation was safe and effective for acute low-back pain, with a strength of evidence level of "B." This agency reviewed all clinical trials available at the time and found no other treatment to have stronger evidence, although nonsteroidal anti-inflammatory drugs received the same "B" rating (131).

A 1997 systematic review of manipulation for low-back pain concluded (132), in contrast to previous opinions (27, 128, 131), that evidence was sufficient to recommend manipulation for chronic back pain but that the evidence for acute back pain was weak. The most recent systematic review (133) used a slightly different method of analysis, taking into account study design, quality, and strength of evidence; these authors concluded that there was moderately strong evidence of a short-term benefit of manipulation for both acute and chronic back pain. They found insufficient evidence for or against the effectiveness of manipulation for sciatica. However, a recent trial found that manipulation for patients with sciatica related to disc herniation was better than chemonucleolysis in the short term and equivalent to that therapy at 12 months (95). A recent quantitative review found only equivocal evidence for the benefit of traction, exercise, and drug therapies for sciatica (134).

The heterogeneity of patients with spinal pain, the

Table 3. **Proposed Mechanisms of Spinal Manipulation**

Action	Mechanism (Reference)
Mechanical/anatomic	Alleviation of an entrapped facet joint inclusion or meniscoid that has been shown to be heavily innervated (138, 139)
Mechanical/anatomic	Repositioning of a fragment of posterior annular material from the intervertebral disc (139, 140)
Mechanical/anatomic	Alleviation of stiffness induced by fibrotic tissue from previous injury or degenerative changes that may include adaptive shortening of fascial tissue (141, 142)
Neurologic/mechanical	Inhibition of excessive reflex activity in the intrinsic spinal musculature or limbs and/or facilitation of inhibited muscle activity (143–145)
Neurologic/mechanical	Reduction of compressive or irritative insults to neural tissues (146)

lack of definitive diagnoses, and the indications in some trials that subgroups of patients appear to respond better to manipulation than others have further highlighted the need to understand the underlying physiologic and psychological mechanisms of pain and disability. The design of rigorous clinical experiments of treatment efficacy for approaches that include strong physician–patient interactions and "hands-on" therapy has been challenging, posing the question of a strong psychological effect of chiropractic treatment. Surprisingly, spinal manipulation is one of the most studied treatments for back pain (56, 132). All manipulation trials, however, have had to contend with design and execution weaknesses that need to be addressed in future studies.

The treatment of disorders not directly related to the musculoskeletal system by manipulation has been supported mainly by clinical experience and case reports. In the past few years, randomized clinical trials for primary dysmenorrhea (115, 116), hypertension (123, 124), chronic asthma (119, 120), enuresis (118), infantile colic (117), and premenstrual syndrome (121) have been completed, with variable results. Two systematic reviews, one on extant trials at the time (135) and a recent one on asthma sponsored by the Cochrane Collaboration (136), concluded that the results do not argue convincingly for or against the utility of spinal manipulation for these kinds of conditions.

Biological Rationale

Chiropractors direct spinal manipulation to a dysfunctional joint "lesion" known as a subluxation. This is characterized as a form of joint strain or sprain with clinically associated hypomobility, malalignment, local and referred pain, inflammation, and muscle tension (137). Subluxation in the chiropractic context primarily connotes a functional and not necessarily an anatomic entity. At least five mechanical and neurologic mechanisms have been proposed (Table 3).

Chiropractic theory has held that subluxation and manipulation can have important physiologic effects: increased range of joint motion (147, 148), changes in facet joint kinematics (149), increased pain tolerance (150), increased muscle strength (151), attenuation of α-motoneuron activity (152), enhanced proprioceptive behavior (153), and changes in β-endorphins (154) and substance P (155). A biomechanical picture of manipulation is beginning to emerge from studies on the forces involved and the resultant kinetics and kinematics (156, 157).

Risks of Spinal Adjustments and Manipulations

The topic of complications from spinal manipulation has been controversial (126, 158, 159). Nonserious side effects of manipulation may consist of localized discomfort, headache, or fatigue that resolves within 24 to 48 hours (160). The more serious reported complications are the cauda equina syndrome from lumbar manipulation and cerebrovascular artery dissection from cervical manipulation. The apparent rarity of these accidental events has made it difficult to assess the magnitude of the complication risk. No serious complication has been noted in more than 73 controlled clinical trials or in any prospectively evaluated case series to date.

Serious complications from lumbar spinal manipulation are extremely rare, estimated to be 1 case per 100 million manipulations (27). For cervical manipulation, the risk for a cerebrovascular accident has been calculated by various authors to range from 1 in 400 000 (161) to between 3 and 6 per 10 million manipulations (126). The figures have been primarily based on retrospectively collected single case reports (126, 158) and unsubstantiated practitioner surveys (161, 162). One retrospective cohort study examined the incidence of cerebrovascular accidents after manipulation (163). It covered the experience of 99% of the practicing chiropractors in Denmark from 1978 to 1988. During this 10-year period, five cases and one death were identified, representing approximately one serious complication for every 1 million cervical manipulations. Unfortunately, there do not appear to be any specific risk factors for vertebrobasilar artery dissection after manipulation, and the cases might represent idiosyncratic events or the aggravation of arterial dissections in progress (159).

THE FUTURE

Significant challenges for conducting high-quality studies in the chiropractic profession continue to exist, but this is changing. The U.S. Health Resources and Services Administration's Chiropractic Demonstration Program was the first federal effort to facilitate collaborative research between chiropractic and medical institutions in 1994, and it continues to sponsor annual conferences designed to set research agenda (164). In 1997, the National Center for Complementary and Alternative Medicine initiated a research center, the Consortial Center for Chiropractic Research, at Palmer College of Chiropractic in Davenport, Iowa. It represents a collaboration of six chiropractic colleges and four state-supported universities.

Chiropractic has survived, and it has begun to embrace the values and behaviors of a mainstream health profession. In the past few decades, chiropractic has strengthened its educational system; initiated research that has validated spinal manipulation; increased its market share of satisfied patients; initiated collaborations with other disciplines in practice, research, and professional settings; and effectively used political, legislative, and legal measures to secure a role. Nevertheless, significant attitudinal and structural barriers to mainstream status still hinder chiropractic, and the advances of recent years may not be enough to ensure continuing progress in this direction.

Chiropractic still maintains some vestiges of an alternative health care profession in image, attitude, and practice. The profession has not resolved questions of professional and social identity, and it has not come to a consensus on the implications of integration into mainstream health care delivery systems and processes. In today's dynamic health care milieu, chiropractic stands at the crossroads of mainstream and alternative medicine. Its future role will probably be determined by its commitment to interdisciplinary cooperation and science-based practice.

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SERIES IN PRIMARY CARE INTERNAL MEDICINE

REVIEW

Evaluation and Management of HIV-Infected Women

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The rate of newly diagnosed AIDS in the United States is increasing fastest in women, who are infected with HIV primarily through heterosexual transmission. Approximately 60% of these women are African American, and 18% are Latina. A gynecologic infection is the most common symptom that leads to initial medical evaluation. Specific studies at baseline should include CD4 lymphocyte count, HIV-1 RNA level, and gynecologic examination with Papanicolaou smear. Decisions about initiation of antiretroviral therapy depend on the patient's clinical diagnoses, her willingness to adhere to treatment, and CD4 lymphocyte and HIV-1 RNA levels. Levels of HIV-1 RNA may be somewhat lower in women than in men at the same CD4 count, whereas women have higher CD4 lymphocyte counts at the time of AIDS diagnosis. However, prospective trials have not yet indicated the need to change the threshold CD4 lymphocyte counts or HIV-RNA levels for initiation of therapy in women. The efficacy of antiretroviral therapy appears to be similar in men and women, although women are more likely to experience toxicities. Abnormal Papanicolaou smears occur in approximately 40% of women at baseline, and 58% are infected with human papillomavirus. The prevalence of both conditions increases with lower CD4 lymphocyte counts and higher HIV-1 RNA levels. Precursor lesions to cervical cancer may be effectively treated, but almost 50% recur within 1 year, mandating careful follow-up. Referral should be sought for specialized gynecologic care and for issues related to HIV itself, since survival is prolonged in patients treated by physicians who are experienced in treating HIV. When they are provided the same access to care, HIV-infected women have similar prognoses as HIV-infected men.

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A 32-year-old African-American woman comes to see you because she has had recurrent vaginitis in the past year. She is concerned because the vaginal discharge has recurred only 2 months from the last episode. She has had six sexual partners in the past 10 years, has been married for 5 years, and is monogamous. She has a 4-year-old son who is active and well. She has never used illicit injection drugs and has never had a blood transfusion.

IS THIS PATIENT TYPICAL OF WOMEN WITH HIV INFECTION, AND SHOULD SHE BE TESTED FOR HIV?

The patient is typical of women with HIV infection; she should be counseled and then tested. The rate of AIDS in the United States is increasing fastest among women, who accounted for approximately 7% of AIDS cases in 1985, 22% in 1997, and 30% in 1999 (1–3). The majority of U.S. women with AIDS belong to ethnic minority groups; African Americans account for 62% of cases, and Latinas and Caucasian persons each account for approximately 18% (3).

Pelvic examination reveals a thick white cervical discharge, no masses, and no tenderness on cervical motion. Microscopic examination of the discharge reveals white cells and hyphae. Cervical cultures are ordered, and you prescribe a 3-day course of topical antifungal therapy. The patient is counseled about HIV and agrees to be tested; results confirm the presence of HIV infection.

WHAT IS THIS WOMAN'S PROBABLE SOURCE OF HIV INFECTION?

The patient was probably infected by heterosexual contact, which is now the most common mode of transmission in U.S. women (2, 3). Because HIV infection may be asymptomatic for up to a decade after initial infection, it would not be unusual for the patient to have been unaware of her partners' HIV status.

SHOULD THE PATIENT'S HUSBAND AND SON BE TESTED FOR HIV?

The patient's husband and son should be tested. The chance of heterosexual transmission increases with higher HIV-1 viral load in the positive partner (4); presence of reproductive tract infections (5, 6), cervical ectopy (7), sex during menstruation (8), and lack of circumcision in the male partner (9) may also increase the likelihood of transmission (10). The risk for vertical transmission from an infected mother (not taking antiretroviral therapy) to her infant is approximately 25%; HIV can be transmitted to the child in utero (11), at birth (12–14), or by breast feeding (15–20).

The patient's husband was seen by another physician and was found to be infected with HIV. His CD4 lymphocyte count was 0.65×10^9 cells/L, and his HIV viral load was 2033 copies/mL. Their son was found to be negative for HIV antibody, and his HIV RNA level was nondetect-

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Table 1. **Treatment of Gynecologic Infections in HIV-Infected Women**

Infection	Treatment
Vaginitis	
Candidiasis	Intravaginal miconazole suppository, 200 mg × 3 d, or 2% cream × 7 days OR Clotrimazole cream (1%) × 7–14 d, or 100 mg/d orally × 7 d, or 500 mg/d orally × 1 d OR Fluconazole, 150 mg/d orally × 1 d
Trichomoniasis	Metronidazole, 2.0 g orally
Bacterial vaginosis	Metronidazole, 500 mg orally twice daily × 7 d
Chlamydia trachomatis	Doxycycline, 100 mg orally twice daily × 7 d OR Azithromycin, 1 g or 1.2 g (two 600-mg tabs) orally × 1
Pelvic inflammatory disease	
Outpatient	Ceftriaxone, 250 mg intramuscularly, or cefoxitin, 2 g intramuscularly, plus probenecid, 1 g orally, followed by doxycycline, 100 mg orally twice daily × 14 d
Hospitalized patients	Cefoxitin, 2 g intravenously every 6 h, plus doxycycline, 100 mg every 12 h, until improved, followed by doxycycline, 100 mg orally twice daily to complete 14 d
Herpes simplex	
Mild	Acyclovir, 400 mg orally three times daily × 7–10 d OR Famciclovir, 250 mg orally three times daily × 7–10 d OR Valacyclovir, 1 g orally twice daily × 7–10 d
Severe or refractory	Acyclovir, 800 mg orally 5 times daily × 7–10 d OR Acyclovir, 5–10 mg/kg of body weight intravenously every 8 h × 7–10 d OR Valacyclovir, 1 g orally twice to three times daily × 7–10 days
Human papillomavirus genital warts	Podophyllin, trichloroacetic acid, cryotherapy
Gonorrhea	Ceftriaxone, 125–250 mg intramuscularly once, OR Spectinomycin, 2 g intramuscularly once
Syphilis	
Early	Benzathine penicillin G, 2.4 million U intramuscularly once
Late	Benzathine penicillin G, 2.4 million U intramuscularly three times weekly
Neurosyphilis	Aqueous penicillin G, 18–24 million U intravenously daily × 10–14 days (3–4 million U every 4 h)

able. The patient's vaginal cultures, which you ordered to rule out other infections, are positive for Candida *organisms.*

SHOULD YOU ALTER THE PRESCRIBED TREATMENT, IN LIGHT OF THE PATIENT'S HIV STATUS?

In general, the patient should receive the same treatment as an HIV-negative woman with candidal vaginitis, although the duration of topical therapy may be extended to 7 to 14 days in the presence of underlying HIV infection. Table 1 shows recommended therapy for common gynecologic infections in HIV-infected women (21, 22).

ARE GYNECOLOGIC INFECTIONS A COMMON INITIAL PRESENTATION IN HIV-INFECTED WOMEN?

The most common reason that HIV-infected women first seek medical attention is development of a gynecologic infection (23). Recurrent candidal vaginitis was the reason for seeking care in 37% of 200 women in one study (23) and has been reported in 3% to 71% of women in published series (24–28); it tends to be seen at relatively high CD4$^+$ T-cell counts (29, 30). No firm evidence indicates that vaginal infections with *Candida* species are more severe in HIV-infected women than in noninfected women, but vulvovaginal candidiasis that is persistent, frequent, or poorly responsive to therapy is considered a clinical category B condition by the Centers for Disease Control and Prevention (31). Gynecologic infections have been diagnosed at a routine study visit in up to 63% of women known to be HIV infected (32) and in 83% at the time of hospitalization, although only 9% were actually hospitalized for a primary gynecologic symptom or diagnosis (32, 33). The presence of infections other than bacterial vaginosis should alert the health care provider to the need for counseling and testing for HIV infection.

Infection with human papillomavirus (HPV) is also common. Compared with 434 HIV-seronegative women at high risk for HIV infection, only HPV infection was statistically more common among the 851 HIV-seropositive women (28% vs. 64%, respectively) (24). Bacterial vaginosis was common in both groups (approximately 34% of patients in each group), and trichomoniasis was diagnosed in 12% of the HIV-infected women (24). Chronic genital infection with herpes simplex virus may be the first manifestation of

Table 2. **Initial Assessment of HIV-Positive Women**

- Comprehensive history and physical examination
  - Gynecologic examination with Papanicolaou smear
  - Discussion of safe sex practices and sexual health
- Laboratory tests
  - Complete blood count
  - Chemistry panel
  - Antibody for hepatitis B and C
  - Antibody for toxoplasmosis
  - Antibody for cytomegalovirus
  - VDRL and rapid plasma reagin tests for syphilis
  - Lipid panel before institution of protease inhibitor therapy
  - Pregnancy test, if indicated
- Other
  - Purified protein derivative skin test (Mantoux, 5 tuberculin units)
  - Chest radiography

AIDS in women (34). Gonorrhea and infection with *Chlamydia trachomatis* are relatively uncommon (24, 33, 35).

The presentation of pelvic inflammatory disease may be more subtle than usual in HIV-infected women; these patients may have less severe pain and lower leukocyte counts (36, 37). However, body temperature may be higher, and an increased incidence of tubal ovarian abscesses has been reported (38). More intensive therapy for pelvic inflammatory disease is often recommended, with use of parenteral antibiotics (21, 22).

Because your patient has newly diagnosed HIV infection, you order screening blood tests and other baseline evaluations.

WHAT BASELINE TESTS SHOULD BE DONE IN WOMEN WITH NEWLY DIAGNOSED HIV INFECTION?

Screening blood work should include a complete blood count, with special attention to the hemoglobin and platelet counts (**Table 2**). Anemia was found in 37% of 2056 HIV-infected women studied as part of the Women's Interagency HIV Study (39). Factors independently associated with anemia included African American ethnicity, mean corpuscular volume of erythrocytes less than 80 fl, CD4 lymphocyte count less than 0.2×10^9 cells/L, higher HIV RNA levels in plasma, current use of zidovudine, and history of a clinical AIDS-defining condition (39). Anemia has been associated with decreased survival in HIV-infected persons (40–43). Thrombocytopenia is also common: It occurs in approximately 40% of patients during the course of infection and is the first manifestation of HIV in 10% (44, 45).

Serum chemistry panels, including glucose, and baseline levels of cholesterol and triglycerides are valuable because many HIV-infected patients eventually receive multiple medications, many of which cause renal, liver, or metabolic toxicity. In addition, up to 75% of HIV-infected patients have abnormal liver enzyme levels on initial evaluation (46).

The U.S. Public Health Service/Infectious Diseases Society of America guidelines suggest initial screening for hepatitis B and C. Hepatitis B vaccination should be considered in patients who do not show immunity to the virus. Co-infection by hepatitis C virus and HIV has been associated with increased levels of hepatitis C virus RNA (47) and more rapid progression of HIV disease (48).

A VDRL or rapid plasma reagin test should be ordered because of the high likelihood of co-infection by HIV and syphilis (49). Biological false-positive results on these tests may be seen in up to 6% of HIV-infected patients (46). Treponemal and nontreponemal tests should be interpreted in the usual manner (22).

An initial assessment of toxoplasmosis IgG can determine the potential risk for reactivation of latent infection (50) and the potential need for future prophylaxis against toxoplasmosis (51). A positive result for toxoplasmosis on IgG antibody testing may also aid in the differential diagnosis of central nervous system disease later in the course of HIV infection (50).

Antibody screening for cytomegalovirus is suggested, since absence of previous cytomegalovirus infection might aid in future decisions about prophylaxis against cytomegalovirus in the setting of severe CD4 lymphocyte depletion ($<0.5 \times 10^9$ cells/L) and might identify patients who should receive cytomegalovirus antibody–negative or leukocyte-depleted blood cell products (51).

A purified protein derivative skin test should be done (Mantoux, 5 tuberculin units); a positive result is 5 mm of induration (52). The purified protein derivative test should be repeated annually in HIV-infected persons at risk for tuberculosis, since the chance of reactivation is approximately 7% to 10% per year (53). Baseline chest radiography is also suggested (54).

A gynecologic examination with Papanicolaou (Pap) smear should be performed at baseline, repeated at 6 months, and then repeated annually, as long as results are normal (51). A pregnancy test should be considered.

Table 3. **Indications for Initiation of Antiretroviral Therapy from the U.S. Public Health Service, Department of Health and Human Services***

Clinical Category	CD4 Lymphocyte Count, $\times 10^9$ *cells/L*	Plasma HIV-1 RNA Level, *copies/mL*	Recommendation
AIDS	Any value	Any value	Treat
Symptomatic HIV Infection or AIDS	Any value	Any value	Treat
Asymptomatic	≤0.35	Any value	Treatment usually offered; may delay in patients with HIV-1 RNA level <20 000 copies/mL
Asymptomatic	>0.35	>30 000 on branched DNA assay or >55 000 on reverse transcription polymerase chain reaction	Some controversy; either treat or defer and monitor CD4 lymphocyte count

* Data from reference 61.

Because your patient has newly diagnosed HIV infection, you order measurements of viral load (HIV-1 RNA level) and CD4 lymphocytes in the blood. One month after resolution of candidal vaginitis, the CD4 lymphocyte count is 0.279×10^9 *cells/L and the HIV viral load is 134 000 copies/mL.*

After discussing the critical importance of adherence to HIV treatment and assessing the patient's willingness to do so, you initiate antiretroviral therapy with zidovudine plus lamivudine (Combivir [Glaxo SmithKline, Research Triangle Park, North Carolina]) and efavirenz.

WHAT FACTORS SHOULD BE CONSIDERED WHEN DECIDING TO INITIATE ANTIRETROVIRAL THERAPY?

Before considering the biological factors that influence the decision to begin antiretroviral therapy, the patient's acceptance of such therapy and her willingness and ability to take all medicines properly must be determined. Lack of almost perfect adherence to antiretroviral therapy has been associated with development of drug resistance and resultant drug failure (55–57). Before starting a specific therapeutic regimen, it is critical to determine whether the patient is willing to adhere to the requirements of such therapy.

The HIV-1 viral load and CD4 lymphocyte count are important biological factors that help guide treatment decisions. The amount of HIV-1 RNA in plasma is directly related to the probability of progression to clinical AIDS in the subsequent 5 years (58, 59). As initially reported in the Multicenter AIDS Cohort Study, a viral load less than 5000 copies/mL on branched DNA testing or less than 10 000 copies/mL on reverse transcriptase polymerase chain reaction is associated with an 8% risk for progression to AIDS in the subsequent 5 years, but an HIV RNA level greater than 36 000 copies/mL is associated with a 5-year risk for progression to AIDS of 62% (59). Current Public Health Service/Department of Health and Human Services guidelines (60) for initiation of antiretroviral therapy (**Table 3**) are somewhat more conservative than previous guidelines (61) in terms of the threshold level of HIV-1 RNA at which treatment should be considered in asymptomatic patients with higher CD4 cell counts ($>0.35 \times 10^9$ cells/L). These changes are based on the acknowledgment that HIV infection is currently incurable and that antiretroviral therapy is associated with significant toxicity and difficulty in terms of adherence.

The CD4 lymphocyte count also provides useful information for determining the need for antiretroviral therapy. Antiretroviral therapy should be initiated in asymptomatic patients with CD4 lymphocyte counts less than 0.35×10^9 cells/L (60, 61). When the CD4 lymphocyte count is less than 0.2×10^9 cells/L or 14%, the risk for AIDS-defining opportunistic infections or neoplasms increases substantially, a condition termed *immunologic AIDS* (31). In patients with immunologic AIDS, prophylaxis against various infections should be initiated, as outlined in **Table 4** (51, 62, 63).

Measurement of viral load and CD4 lymphocyte count provides further prognostic information; the risk for AIDS increases in a stepwise manner as the CD4 lymphocyte count decreases to less than 0.5, 0.35, and 0.2×10^9 cells/L at the same HIV RNA level (64). These data have led to the development of guidelines for initiation of therapy in HIV-infected persons (**Table 3**).

Since the patient in this hypothetical case is eager to begin treatment and since her viral load is high (with CD4 lymphocyte count $<0.35 \times 10^9$ cells/L), it is reasonable to initiate antiretroviral therapy with three agents, including two reverse-transcriptase inhibitors (zidovudine and lamivudine) and a third reverse-transcriptase inhibitor (abacavir), a non-nucleoside reverse-transcriptase inhibitor (efavirenz), or a protease inhibitor (**Table 5**). The antiretroviral regimen should be chosen on the basis of its complexity in terms of numbers of pills and the frequency of dosing, as well as potential toxicities and drug interactions. Combivir consists of only one pill taken twice daily, and efavirenz is taken once daily; there are no restrictions on food intake for either medication. The combination is known to be efficacious and may avoid the potential complication of

Table 4. **Abbreviated Recommendations from the U.S. Public Health Service for Use of Prophylactic Antimicrobial Agents***

Infection	Threshold for Initiation of Prophylaxis	Agent Used as Prophylaxis	Criteria for Discontinuation of Prophylaxis
Pneumocystis carinii pneumonia	CD4 lymphocyte count $<0.2 \times 10^9$ cells/L Previous *P. carinii* infection HIV-related thrush Fever of unknown origin for 2 weeks	Trimethoprim, 160 mg + sulfamethoxazole, 800 mg/d OR Dapsone, 100 mg/d OR Aerosolized pentamidine, 300 mg/mo by Respirgard II nebulizer† OR Atovaquone, 750 mg orally twice daily with meals	Patients with increases of CD4 lymphocyte count to $>0.2 \times 10^9$ cells/L for 3–6 months may safely discontinue *P. carinii* prophylaxis
Toxoplasma gondii	CD4 lymphocyte count $<0.1 \times 10^9$ cells/L and positive result for *T. gondii* on IgG antibody testing	Trimethoprim, 160 mg + sulfamethoxazole, 800 mg/d OR Dapsone, 50 mg + pyrimethamine, 50 mg/wk + leucovorin, 25 mg/wk OR Dapsone, 200 mg/wk orally + pyrimethamine, 75 mg/wk + leucovorin 25 mg/wk orally	May discontinue primary prophylaxis when CD4 lymphocyte count is $>0.1 \times 10^9$ cells/L for ≥3–6 months
Mycobacterium avium complex	CD4 lymphocyte count $<0.5 \times 10^9$ cells/L	Clarithromycin, 500 mg orally twice daily OR Azithromycin, 1200 mg/wk orally OR Rifabutin, 300 mg/d orally OR Azithromycin, 1200 mg/wk + rifabutin, 300 mg/d orally	May discontinue prophylaxis if CD4 lymphocyte count is $>0.1 \times 10^9$ cells/L for 3–6 months in patients without previous *M. avium* complex bacteremia
M. tuberculosis	Positive result on purified protein derivative test (≥5 mm of induration) or recent contact with person with tuberculosis	Isoniazid (INH), 300 mg/d + pyridoxine, 50 mg/d for ≥270 doses (9 mo or up to 12 mo with interruption) OR Isoniazid, 900 mg + pyridoxine, 100 mg twice weekly with directly observed therapy to ≥76 doses (9 mo or up to 12 mo with interruption) OR In patients not receiving a protease inhibitor or non-nucleoside reverse transcriptase inhibitor: rifampin, 600 mg/d + pyrazinamide, 20 mg/kg of body weight daily for ≥60 doses (2 mo or up to 3 mo with interruptions)	
Streptococcus pneumoniae	All patients	Pneumovax‡, one 0.5-mL dose; consider revaccination at 5 years or at time of CD4 cell count increase to $>0.2 \times 10^9$ cells/L, if initial vaccination occurred at CD4 cell count is $<0.2 \times 10^9$ cells/L	
Hepatitis B	Negative result on anti-hepatitis B core screening test	Recombivax HB‡, 10 μg intramuscularly × 3 doses, OR Energix-B§, 20 μg intramuscularly × 3 doses	
Influenza	All patients	Influenza vaccine, 0.5 mL intramuscularly; repeat annually	
Varicella	Exposure to chicken pox or herpes zoster in patients negative by history or antibody to varicella	Varicella zoster immune globulin, 5 vials (6.25 mL) intramuscularly within 48–96 hours of exposure	

* Information from reference 63.
† Manufactured by Marquest Medical Products, Inc., Englewood, Colorado.
‡ Manufactured by Merck & Co., West Point, Pennsylvania.
§ Manufactured by GlaxoSmithKline, Research Triangle Park, North Carolina.

Table 5. **Available Antiretroviral Agents**

Class	Drug	Dosing	Comments
Nucleoside reverse transcriptase inhibitors	Zidovudine	300 mg twice daily	
	Didanosine	Weight $\geq$ 60 kg: 200 mg twice daily or 400 mg/d; weight $<$ 60 kg: 125 mg twice daily or 250 mg/d	Pills must be chewed; empty stomach; powder also available
	Lamivudine	150 mg twice daily	2 mg/kg of body weight twice daily for weight $<$50 kg
	Stavudine	40 mg twice daily; 30 mg twice daily if $<$60 kg; 20 mg twice daily with peripheral neuropathy	Should not be used with zidovudine
	Dideoxycytidine	0.75 mg three times daily	
	Abacavir	300 mg twice daily	
	Combivir* (zidovudine + lamivudine)	1 tab twice daily	
	Trizivir* (zidovudine + lamivudine + abacavir)	1 tab twice daily	
Non-nucleoside reverse transcriptase inhibitors	Nevirapine†	200 mg twice daily	Start with 200 mg/d × 14 d to avoid rash
	Delaviradine‡	400 mg three times daily	Separate dosing of didanosine or antacids by 1 h
	Efavirenz	600 mg/d	Take at bedtime to reduce early central nervous system side effects
Nucleotide reverse transcriptase inhibitors	Tenofavir§	300 mg/d	Take with food
Protease inhibitors	Ritonavir†	600 mg twice daily	Dosage of 100–400 mg twice daily when used with another protease inhibitor; increase initial doses over first 14 days for gastrointestinal tolerance
	Saquinavir (Invirase)‡‖	400 mg twice daily with ritonavir, 400 mg twice daily	
	Saquinavir (Fortovase)‡	1200 mg three times daily	Preferred because of better oral bioavailability
	Indinavir	800 mg every 8 h	Take while fasting or with light, nonfat meal; must drink $\geq$48 oz of fluids daily to prevent renal stones
	Nelfinavir†	750 mg three times daily or 1250 mg twice daily	Take with food
	Amprenavir†	1200 mg twice daily	
	Kaletra (lopinavir + ritonavir)†¶	3 capsules twice daily (133.3/33.3 mg)	

* Manufactured by Glaxo SmithKline, Research Triangle Park, North Carolina.
† These drugs should not be used with oral contraceptive pills, since they result in decreased ethinyl estradiol levels and increased risk for pregnancy.
‡ No information is available on interactions with oral contraceptives.
§ Manufactured by Gilead Sciences, Inc., Foster City, California.
‖ Manufactured by Roche Laboratories, Nutley, New Jersey.
¶ Manufactured by Abbott Laboratories, North Chicago, Illinois.

lipodystrophy, reported primarily with use of protease inhibitors (65). The ease of administration may facilitate adherence to therapy.

ARE INDICATIONS FOR ANTIRETROVIRAL THERAPY THE SAME IN MEN AND WOMEN?

During pregnancy, antiretroviral therapy is routinely advised in an attempt to prevent vertical transmission of HIV (66, 67). Aside from this circumstance, the recommendations for initiation of antiretroviral therapy are similar for men and women (60, 61). However, the threshold CD4 lymphocyte counts and HIV-1 RNA levels for initiation of antiretroviral therapy are somewhat controversial and may differ between men and women. The CD4 lymphocyte count may be higher at the time that AIDS is first diagnosed in women versus men (68), suggesting that antiretroviral therapy should perhaps be initiated at a lower threshold value in women. Furthermore, the level of HIV-1 RNA in plasma may be lower in women than in men at similar CD4 lymphocyte counts (69–74), and lower HIV-1 RNA levels have been associated with progression to AIDS in women (71, 73, 74). Although not all studies have confirmed these findings (75, 76), the bulk of current evidence indicates a real difference in the level of HIV-1 RNA associated with disease progression in men versus women. Since women appear to have lower RNA levels (69–74) and higher CD4 lymphocyte counts when AIDS is first diagnosed (68), it is possible that women should be treated earlier in the course of infection. Prospective clinical trials are required to address this matter.

WHAT IS THE EFFICACY AND TOXICITY OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN HIV-INFECTED WOMEN COMPARED WITH MEN?

Most studies indicate that the efficacy of antiretroviral therapy is equivalent in women and men (77–83). Ritonavir in combination with reverse transcriptase inhibitors has been studied in 90 women and 996 men (77). Although the efficacy of the drug appeared to be similar in both groups, women were more likely than men to experience nausea (63% vs. 56%), vomiting (49% vs. 31%), malaise and fatigue (47% vs. 34%), and numbness and tingling around the mouth (37% vs. 27%). In contrast, men were more likely than women to experience diarrhea (62% vs. 49%). Use of antiretroviral therapy, especially protease inhibitors, has also been associated with abnormal accumulations of body fat and elevated cholesterol, triglyceride, and glucose levels, with development of insulin resistance (65, 84–88). These abnormalities, which represent more than a single entity, are termed *the lipodystrophy syndrome.* Women with the lipodystrophy syndrome (87) are more likely than men to experience increases in abdominal fat (93% vs. 76%) and breast size (74% vs. 31%), whereas men are more likely than women to develop lipoatrophy in the limbs (69% vs. 53%) and buttocks (60% vs. 45%). Men are also more likely than women to develop elevated levels of triglycerides (63% vs. 26%) and cholesterol (50% vs. 26%).

A retrospective review of 200 men and 76 women attempted to ascertain the value of highly active antiretroviral therapy (HAART) regimens in a "real-world" clinical setting (79). At 7 to 14 months after initiation of a HAART regimen containing a protease inhibitor, 37% of patients had nondetectable plasma HIV-1 RNA levels; the regimen's effectiveness did not differ significantly in men and women. However, women had a statistically increased risk for adverse drug effects compared with men (37% vs. 25%) ($P = 0.008$). Of the protease inhibitors, ritonavir had a higher toxicity profile compared with indinavir or nelfinavir; adverse effects consisted primarily of gastrointestinal symptoms.

These data indicate that various antiretroviral agents and combinations are equally efficacious in HIV-infected men or women, although the toxicity profiles may differ.

The patient and her husband do not wish to have more children, and she has been taking oral contraceptives for birth control. She asks if the HAART that you have prescribed will interfere with these oral contraceptives.

ARE THERE ANY KNOWN DRUG INTERACTIONS BETWEEN HAART AND ORAL CONTRACEPTIVES?

Drug interactions may be complex, especially when protease inhibitors are involved (21, 89, 90). Several antiretroviral agents interfere with metabolism of oral contraceptives and should be avoided (**Table 5**). Because efavirenz may be associated with severe birth defects (91), it is critical to discuss the importance of effective contraceptive measures while patients are taking efavirenz.

You measure the patient's HIV-1 viral load after 1 and 3 months and find that the level is now nondetectable (<0.5 copies/mL), while the CD4 lymphocyte count has increased to 0.499 × 10^9 cells/L. Serologic testing for hepatitis, toxoplasmosis, cytomegalovirus, and syphilis is negative, and the tuberculosis skin test is nonreactive. The patient has no anemia or thrombocytopenia, and her liver and renal functions are normal. You ask her to continue taking her antiretroviral medications and to return in 3 months.

HOW OFTEN SHOULD HIV-1 RNA LEVELS AND CD4 LYMPHOCYTE COUNTS BE RECHECKED?

The CD4 lymphocyte count and HIV-1 RNA levels should be measured every 3 to 4 months. The same laboratory and testing methods should be used. In the case of markedly divergent results, the tests should be repeated to ensure their accuracy. Any persistent increase in HIV-1 RNA viral load greater than 0.3 $\log_{10}$ (50% or more) is considered significant, warrants further evaluation, and may indicate the need to change antiretroviral therapy. Follow-up HIV-1 RNA measurements should be obtained when the patient is clinically stable and has had no intercurrent infection or immunization within the past 4 weeks, both of which may transiently increase the viral load (92–94).

At the patient's next quarterly evaluation, her HIV-1 RNA level is still nondetectable and her CD4 lymphocyte count is 0.501 × 10^9 cells/L. The patient states that she

Table 6. **Guidelines for Performance of Follow-up Papanicolaou Smears and Colposcopy in HIV-Infected Women***

Baseline Abnormality	Recommended Follow-up
Normal Pap smear	Repeat in 6 mo, then annually
Severe inflammation	Evaluate for infection: repeat Pap smear in 2–3 mo
ASCUS or atypia	Repeat Pap smear every 6 mo until 3 consecutive negative smears; then yearly follow-up Colposcopy with second report of ASCUS
Low-grade squamous-cell intraepithelial lesion or low-grade cervical intraepithelial neoplasia (CIN I)	Pap smear every 6 mo, and colposcopy with directed biopsy if repeated Pap smear is abnormal; some clinicians proceed directly to colposcopy, especially if patient is likely to be lost to follow-up
High-grade squamous intraepithelial lesion or high-grade cervical intraepithelial neoplasia (CIN II or III)	Colposcopy with biopsy followed by definitive therapy (conization or loop excision) and follow-up every 6 mo; careful examination for squamous intraepithelial lesions at other anogenital sites

* Information from reference 21. ASCUS = atypical squamous cells of uncertain significance; Pap = Papanicolaou.

feels well, with no intercurrent vaginitis. You explain the importance of obtaining a Pap smear now that the vaginitis has cleared.

The patient's gynecologic examination is normal, but the Pap smear is abnormal, showing a Bethesda system low-grade squamous intraepithelial lesion.

Do HIV-Infected Women Commonly Have Abnormal Pap Smears?

Abnormal Pap smears are common in HIV-infected women; they were documented in 40% of 2054 HIV-positive women and 17% of HIV-negative women in the Women's Interagency HIV Study cohort (95). Abnormal Pap smears are associated with HIV infection, CD4 lymphocyte count less than 0.2×10^9 cells/L, HPV infection, and infection with high-risk types or multiple types of HPV (95). The relationship between HIV infection (96–99) or lower CD4 lymphocyte counts (100) and increased likelihood of cervical intraepithelial neoplasia (CIN) is well documented. Higher HIV-1 RNA levels have also been associated with increased risk for CIN (101).

Should the Patient Undergo Testing for HPV?

Since the patient has an abnormal Pap smear, you elect to test her for presence and type of HPV infection by using polymerase chain reaction for HPV DNA.

Infection with HPV is common in HIV-infected women; in one study, it was detected in 58% of 2015 seropositive women and 26% of matched seronegative controls (102). The prevalence of HPV is even higher in women with CD4 lymphocyte counts less than 0.2×10^9 cells/L (103) and those with high HIV-1 viral load (102). Of note, HIV-infected women are also likely to have persistent HPV infection over time (104, 105), a factor associated with development of invasive cervical cancer in HIV-negative women (106). Routine testing for HPV in HIV-infected women is not yet recommended.

Why Is HPV Infection Important in Terms of Cervical Cancer?

Aside from its relationship to invasive cervical cancer, HPV is associated with the advanced precursor lesions CIN II and CIN III (107, 108). Multiple types of HPV have been identified, including HPV 6 and 11, which are associated with viral condyloma or mild dysplastic changes (CIN I) that do not progress to frank neoplasia (109). In contrast, HPV types 16, 18, 31, 33, and 35 are often associated with more advanced precursor lesions and are found in most cases of invasive carcinoma (110, 111).

You explain to the patient that her Pap smear does not reveal cervical cancer but that she might have a precancerous lesion, which will require specialized assessment. You refer her to a gynecologist with experience in the care of HIV-infected women. Colposcopy confirms the presence of low-grade cervical intraepithelial neoplasia (CIN I); infection with HPV type 6 is also present.

What Is the Course of CIN in HIV-Infected Women, and How Should CIN Be Treated and Followed?

No specific therapy is required for CIN I, since this grade of lesion may regress spontaneously. However, careful follow-up is required (**Table 6**). If CIN II or III is found on colposcopy, treatment is needed to prevent eventual progression to invasive cervical carcinoma (108). Various therapies are efficacious; loop electrical excision procedure and cervical conization (cone biopsy) are the procedures most commonly performed in HIV-infected women (108). In HIV-negative women with CIN II or III, the risk for persistent CIN or CIN recurring 1 year after specific therapy is approximately 10%, whereas the recurrence rate approaches 40% to 60% in HIV-infected women (112). In preliminary studies, use of 5% topical 5-fluorouracil cream, administered at a dosage of 1 g every 2 weeks for 6 months, has been associated with a statistically significant reduction in recurrence (28% of treated women and 47% of controls) (113). No significant systemic toxicities were observed, and rates of local toxicity were similar in both groups. Other experimental approaches are currently under study.

Since the likelihood of both HPV infection and CIN correlate with HIV-1 viral load and CD4 lymphocyte count, use of HAART may be associated with improvements in the clinical course of HPV or CIN. Although results are conflicting, some studies have shown a significant decrease in the prevalence of CIN after HAART (114, 115).

Your patient remains well. However, approximately 1 year after institution of HAART, her HIV-1 RNA level has increased to 76 000 copies/mL and her CD4 lymphocyte count has decreased to 0.32 × 10^9 cells/L. You repeat these tests in 2 weeks, with similar results. You question her carefully about the possibility of any intercurrent illness or vaccination, which she denies. You explain that her HIV-1 may have become resistant to the medicines she is taking and ask how many times she forgot to take her antiretroviral pills in the past week. She seems uncomfortable and says that she stopped taking her medicines 3 weeks ago because she found it too hard to remember to take them while trying to manage her household.

WHAT IS THE IMPACT OF INADEQUATE ADHERENCE TO ANTIRETROVIRAL MEDICATIONS, AND WHAT LEVEL OF ADHERENCE IS REQUIRED FOR OPTIMAL EFFECT?

Inadequate adherence to antiretroviral therapy may result in development of increasing HIV-1 viral load (55–57, 116, 117), development of antiretroviral drug resistance (118), and decreased survival (118–120). Some studies have shown optimal retroviral suppression at compliance levels as low as 70% (121), although the majority of recent studies indicate that adherence rates of 95% or greater are associated with better outcomes in terms of viral suppression (55–57).

Factors associated with decreased adherence include increasing complexity of the regimen (122), lack of belief that the regimen might work (56, 123), lack of social support, current abuse of alcohol or recreational drugs (56, 124), change in daily routine (125), forgetfulness, higher CD4 lymphocyte counts (56, 123), and psychiatric illness or depression (126–129). Increased experience with HIV disease by the treating physician has been statistically associated with improved patient adherence (129).

Your patient starts to cry, stating that she is extremely depressed and worried about dying, leaving her son as an orphan. She doesn't have enough energy to care for herself and her family properly. She doesn't believe that the medicines will prevent her death from AIDS, and she feels overwhelmed by all of the difficulties in her life.

SHOULD YOUR PATIENT BE REFERRED TO A MENTAL HEALTH PROFESSIONAL? WHICH MANAGEMENT ISSUES SHOULD BE REFERRED TO A SPECIALIST?

Your patient should be referred to a mental health professional. Significant depression has been reported in as many as 60% of HIV-infected women (130), who often feel overwhelmed and exhausted with the burdens of caring for children, running a household, and meeting financial obligations. In these circumstances, HIV-infected women often neglect their own health care, with the inherent difficulties of transportation, cost, and lack of child care facilities, choosing instead to spend their energy caring for children or others who are dependent on them. Professional psychological care would be of benefit, in terms of adherence to medical therapy (129) and other quality-of-life issues.

Referral to other specialists may also be required in other circumstances throughout the course of your patient's care, such as development of specific gynecologic disorders or cancer; decisions and care regarding potential pregnancy; and management of various malignant, hematologic, or other organ-specific complications. Guidance from specialists in HIV disease will also probably be required. Referral to an HIV specialist is indicated if the patient's virologic or immunologic profile suggests failure of therapy or if questions about potential drug toxicities or interactions arise. Patients who receive their care from physicians experienced in HIV disease have been shown to fare better and live longer (131–134).

Your patient expresses her fears about the long-term care of her son. She asks you about her long-term prognosis compared with that of her husband.

DOES THE PROGNOSIS OF HIV INFECTION DIFFER IN WOMEN AND MEN?

Although an improved prognosis for women versus men with HIV infection has been reported (25), most early studies documented significantly shorter survival in women with AIDS (135, 136). When these latter analyses were restricted to patients who were taking antiretroviral therapy, no difference in survival was found between men and women (135). After adjusting for baseline CD4 lymphocyte counts and ensuring that both women and men had the same access to care, Chaisson and colleagues (137) demonstrated conclusively that survival of women with HIV disease was similar to that in men. Others have since confirmed that finding (138, 139). These data suggest that earlier reports of decreased survival in women with HIV or AIDS may have resulted from decreased access to care, a problem that persists among HIV-infected women in the United States (140–144). When used properly, effective antiretroviral therapy has been associated with a reduction in mortality of approximately 50% among patients with AIDS and a reduction in development of clinical AIDS-defining conditions of approximately 75% among patients with HIV (145, 146).

Several books and articles (21, 22, 51, 60, 61, 66, 90) and Web sites (147–150) provide additional details on practical issues in the management of HIV-infected women.

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Medical Professionalism in the New Millennium: A Physician Charter

Project of the ABIM Foundation, ACP–ASIM Foundation, and European Federation of Internal Medicine*

To our readers: I write briefly to introduce the Medical Professionalism Project and its principal product, the Charter on Medical Professionalism. The charter appears in print for the first time in this issue of *Annals* and simultaneously in *The Lancet.* I hope that we will look back upon its publication as a watershed event in medicine. Everyone who is involved with health care should read the charter and ponder its meaning.

The charter is the product of several years of work by leaders in the ABIM Foundation, the ACP–ASIM Foundation, and the European Federation of Internal Medicine. The charter consists of a brief introduction and rationale, three principles, and 10 commitments. The introduction contains the following premise: Changes in the health care delivery systems in countries throughout the industrialized world threaten the values of professionalism. The document conveys this message with chilling brevity. The authors apparently feel no need to defend this premise, perhaps because they believe that it is a universally held truth. The authors go further, stating that the conditions of medical practice are tempting physicians to abandon their commitment to the primacy of patient welfare. These are very strong words. Whether they are strictly true for the profession as a whole is almost beside the point. Each physician must decide if the circumstances of practice are threatening his or her adherence to the values that the medical profession has held dear for many millennia.

Three Fundamental Principles set the stage for the heart of the charter, a set of commitments. One of the three principles, the principle of primacy of patient welfare, dates from ancient times. Another, the principle of patient autonomy, has a more recent history. Only in the later part of the past century have people begun to view the physician as an advisor, often one of many, to an autonomous patient. According to this view, the center of patient care is not in the physician's office or the hospital. It is where people live their lives, in the home and the workplace. There, patients make the daily choices that determine their health. The principle of social justice is the last of the three principles. It calls upon the profession to promote a fair distribution of health care resources.

There is reason to expect that physicians from every point on the globe will read the charter. Does this document represent the traditions of medicine in cultures other than those in the West, where the authors of the charter have practiced medicine? We hope that readers everywhere will engage in dialogue about the charter, and we offer our pages as a place for that dialogue to take place. If the traditions of medical practice throughout the world are not congruent with one another, at least we may make progress toward understanding how physicians in different cultures understand their commitments to patients and the public.

Many physicians will recognize in the principles and commitments of the charter the ethical underpinning of their professional relationships, individually with their patients and collectively with the public. For them, the challenge will be to live by these precepts and to resist efforts to impose a corporate mentality on a profession of service to others. Forces that are largely beyond our control have brought us to circumstances that require a restatement of professional responsibility. The responsibility for acting on these principles and commitments lies squarely on our shoulders.

—*Harold C. Sox, MD, Editor*

Physicians today are experiencing frustration as changes in the health care delivery systems in virtually all industrialized countries threaten the very nature and values of medical professionalism. Meetings among the European Federation of Internal Medicine, the American College of Physicians–American Society of Internal Medicine (ACP–ASIM), and the American Board of Internal Medicine (ABIM) have confirmed that physician views on professionalism are similar in quite diverse systems of health care delivery. We share the view that medicine's commitment to the patient is being challenged by external forces of change within our societies.

Recently, voices from many countries have begun calling for a renewed sense of professionalism, one that

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*This charter was written by the members of the Medical Professionalism Project: ABIM Foundation: Troy Brennan, MD, JD (*Project Chair*), Brigham and Women's Hospital, Boston, Massachusetts; Linda Blank (*Project Staff*), ABIM Foundation, Philadelphia, Pennsylvania; Jordan Cohen, MD, Association of American Medical Colleges, Washington, DC; Harry Kimball, MD, American Board of Internal Medicine, Philadelphia, Pennsylvania; and Neil Smelser, PhD, University of California, Berkeley, California. ACP–ASIM Foundation: Robert Copeland, MD, Southern Cardiopulmonary Associates, LaGrange, Georgia; Risa Lavizzo-Mourey, MD, MBA, Robert Wood Johnson Foundation, Princeton, New Jersey; and Walter McDonald, MD, American College of Physicians–American Society of Internal Medicine, Philadelphia, Pennsylvania. European Federation of Internal Medicine: Gunilla Brenning, MD, University Hospital, Uppsala, Sweden; Christopher Davidson, MD, FRCP, FESC, Royal Sussex County Hospital, Brighton, United Kingdom; Philippe Jaeger, MB, MD, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Alberto Malliani, MD, Università di Milano, Milan, Italy; Hein Muller, MD, PhD, Ziekenhuis Gooi-Noord, Rijksstraatweg, the Netherlands; Daniel Sereni, MD, Hôpital Saint-Louis, Paris, France; and Eugene Sutorius, JD, Faculteit der Rechts Geleerdheid, Amsterdam, the Netherlands. Special Consultants: Richard Cruess, MD, and Sylvia Cruess, MD, McGill University, Montreal, Canada; and Jaime Merino, MD, Universidad Miguel Hernández, San Juan de Alicante, Spain.

is activist in reforming health care systems. Responding to this challenge, the European Federation of Internal Medicine, the ACP–ASIM Foundation, and the ABIM Foundation combined efforts to launch the Medical Professionalism Project (www.professionalism.org) in late 1999. These three organizations designated members to develop a "charter" to encompass a set of principles to which all medical professionals can and should aspire. The charter supports physicians' efforts to ensure that the health care systems and the physicians working within them remain committed both to patient welfare and to the basic tenets of social justice. Moreover, the charter is intended to be applicable to different cultures and political systems.

PREAMBLE

Professionalism is the basis of medicine's contract with society. It demands placing the interests of patients above those of the physician, setting and maintaining standards of competence and integrity, and providing expert advice to society on matters of health. The principles and responsibilities of medical professionalism must be clearly understood by both the profession and society. Essential to this contract is public trust in physicians, which depends on the integrity of both individual physicians and the whole profession.

At present, the medical profession is confronted by an explosion of technology, changing market forces, problems in health care delivery, bioterrorism, and globalization. As a result, physicians find it increasingly difficult to meet their responsibilities to patients and society. In these circumstances, reaffirming the fundamental and universal principles and values of medical professionalism, which remain ideals to be pursued by all physicians, becomes all the more important.

The medical profession everywhere is embedded in diverse cultures and national traditions, but its members share the role of healer, which has roots extending back to Hippocrates. Indeed, the medical profession must contend with complicated political, legal, and market forces. Moreover, there are wide variations in medical delivery and practice through which any general principles may be expressed in both complex and subtle ways. Despite these differences, common themes emerge and form the basis of this charter in the form of three fundamental principles and as a set of definitive professional responsibilities.

FUNDAMENTAL PRINCIPLES

Principle of primacy of patient welfare. This principle is based on a dedication to serving the interest of the patient. Altruism contributes to the trust that is central to the physician–patient relationship. Market forces, societal pressures, and administrative exigencies must not compromise this principle.

Principle of patient autonomy. Physicians must have respect for patient autonomy. Physicians must be honest with their patients and empower them to make informed decisions about their treatment. Patients' decisions about their care must be paramount, as long as those decisions are in keeping with ethical practice and do not lead to demands for inappropriate care.

Principle of social justice. The medical profession must promote justice in the health care system, including the fair distribution of health care resources. Physicians should work actively to eliminate discrimination in health care, whether based on race, gender, socioeconomic status, ethnicity, religion, or any other social category.

A SET OF PROFESSIONAL RESPONSIBILITIES

Commitment to professional competence. Physicians must be committed to lifelong learning and be responsible for maintaining the medical knowledge and clinical and team skills necessary for the provision of quality care. More broadly, the profession as a whole must strive to see that all of its members are competent and must ensure that appropriate mechanisms are available for physicians to accomplish this goal.

Commitment to honesty with patients. Physicians must ensure that patients are completely and honestly informed before the patient has consented to treatment and after treatment has occurred. This expectation does not mean that patients should be involved in every minute decision about medical care; rather, they must be empowered to decide on the course of therapy. Physicians should also acknowledge that in health care, medical errors that injure patients do sometimes occur. Whenever patients are injured as a consequence of medical care, patients should be informed promptly because failure to do so seriously compromises patient and societal trust. Reporting and analyzing medical mistakes provide the basis for appropriate prevention and improvement strategies and for appropriate compensation to injured parties.

Commitment to patient confidentiality. Earning the trust and confidence of patients requires that appropriate confidentiality safeguards be applied to disclosure of patient information. This commitment extends to discussions with persons acting on a patient's behalf when obtaining the patient's own consent is not feasible. Fulfilling the commitment to confidentiality is more pressing now than ever before, given the widespread use of electronic information systems for compiling patient data and an increasing availability of genetic information. Physicians recognize, however, that their commitment to patient confidentiality must occasionally yield to overriding considerations in the public interest (for example, when patients endanger others).

Commitment to maintaining appropriate relations with patients. Given the inherent vulnerability and dependency of patients, certain relationships between physicians and patients must be avoided. In particular, physicians should never exploit patients for any sexual advantage, personal financial gain, or other private purpose.

Commitment to improving quality of care. Physicians must be dedicated to continuous improvement in the quality of health care. This commitment entails not only maintaining clinical competence but also working collaboratively with other professionals to reduce medical error, increase patient safety, minimize overuse of health care resources, and optimize the outcomes of care. Physicians must actively participate in the development of better measures of quality of care and the application of quality measures to assess routinely the performance of all individuals, institutions, and systems responsible for health care delivery. Physicians, both individually and through their professional associations, must take responsibility for assisting in the creation and implementation of mechanisms designed to encourage continuous improvement in the quality of care.

Commitment to improving access to care. Medical professionalism demands that the objective of all health care systems be the availability of a uniform and adequate standard of care. Physicians must individually and collectively strive to reduce barriers to equitable health care. Within each system, the physician should work to eliminate barriers to access based on education, laws, finances, geography, and social discrimination. A commitment to equity entails the promotion of public health and preventive medicine, as well as public advocacy on the part of each physician, without concern for the self-interest of the physician or the profession.

Commitment to a just distribution of finite resources. While meeting the needs of individual patients, physicians are required to provide health care that is based on the wise and cost-effective management of limited clinical resources. They should be committed to working with other physicians, hospitals, and payers to develop guidelines for cost-effective care. The physician's professional responsibility for appropriate allocation of resources requires scrupulous avoidance of superfluous tests and procedures. The provision of unnecessary services not only exposes one's patients to avoidable harm and expense but also diminishes the resources available for others.

Commitment to scientific knowledge. Much of medicine's contract with society is based on the integrity and appropriate use of scientific knowledge and technology. Physicians have a duty to uphold scientific standards, to promote research, and to create new knowledge and ensure its appropriate use. The profession is responsible for the integrity of this knowledge, which is based on scientific evidence and physician experience.

Commitment to maintaining trust by managing conflicts of interest. Medical professionals and their organizations have many opportunities to compromise their professional responsibilities by pursuing private gain or personal advantage. Such compromises are especially threatening in the pursuit of personal or organizational interactions with for-profit industries, including medical equipment manufacturers, insurance companies, and pharmaceutical firms. Physicians have an obligation to recognize, disclose to the general public, and deal with conflicts of interest that arise in the course of their professional duties and activities. Relationships between industry and opinion leaders should be disclosed, especially when the latter determine the criteria for conducting and reporting clinical trials, writing editorials or therapeutic guidelines, or serving as editors of scientific journals.

Commitment to professional responsibilities. As members of a profession, physicians are expected to work collaboratively to maximize patient care, be respectful of one another, and participate in the processes of self-regulation, including remediation and discipline of members who have failed to meet professional standards. The profession should also define and organize the educational and standard-setting process for current and future members. Physicians have both individual and collective obligations to participate in these processes. These obligations include engaging in internal assessment and accepting external scrutiny of all aspects of their professional performance.

SUMMARY

The practice of medicine in the modern era is beset with unprecedented challenges in virtually all cultures and societies. These challenges center on increasing disparities among the legitimate needs of patients, the available resources to meet those needs, the increasing dependence on market forces to transform health care systems, and the temptation for physicians to forsake their traditional commitment to the primacy of patients' interests. To maintain the fidelity of medicine's social contract during this turbulent time, we believe that physicians must reaffirm their active dedication to the principles of professionalism, which entails not only their personal commitment to the welfare of their patients but also collective efforts to improve the health care system for the welfare of society. This Charter on Medical Professionalism is intended to encourage such dedication and to promote an action agenda for the profession of medicine that is universal in scope and purpose.

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EDITORIAL

Stirred, Not Shaken

The effect of alcohol on the cardiovascular system has been studied and debated for over 150 years (1), but a specific cardiomyopathy related to excessive alcohol consumption has been recognized only for the past half century (2). The putative effect of alcohol on the heart has been clouded and confounded by cardiovascular damage due to simultaneous nutritional deficiency as a consequence of beriberi, the toxic effects of additives such as cobalt, and the lack of a good large-animal model of alcoholic cardiomyopathy (3). We now know that alcohol can directly affect the cardiovascular system, but the precise mechanism of damage remains controversial (4, 5). Two studies in this issue (6, 7) add to our understanding of this association. While they may raise almost as many questions as they answer, taken together they can be stirred into our understanding of alcohol's effects on the heart without fundamentally shaking the foundations of our knowledge.

That alcohol can affect the heart in humans would seem to be beyond doubt, although some would argue that a firm causal relationship has not been proven (8). Clear and persuasive data show that long-term alcohol use may be associated with left ventricular dysfunction and overt congestive heart failure, a variety of supraventricular and ventricular arrhythmias, sudden death, and hypertension. Alcohol is believed to be the causal agent in 3% to 40% of all patients with otherwise unexplained (idiopathic) dilated cardiomyopathy (9). Even short-term, acute ingestion of alcohol may result in transient left ventricular dysfunction and arrhythmias (10, 11). The cessation of alcohol consumption in patients with presumed alcoholic cardiomyopathy is associated with an improvement in left ventricular function and a reduction in scintigraphic evidence of myocardial damage (12). Long-term alcohol consumption produces a pattern of dilated cardiomyopathy in several animal models, although the lack of a good large-animal model has hindered study (3, 4). The recent description of a stable avian model of alcoholic cardiomyopathy may accelerate progress in our understanding of alcohol-mediated cardiovascular damage (3).

In this issue, Nicolás and colleagues further document improved left ventricular function with the reduction or cessation of alcohol consumption, as well as a progressive worsening of left ventricular function in patients who continue to drink heavily (6). In a 4-year prospective study, the authors found that persons with chronic alcoholism who continued to drink heavily demonstrated progressive deterioration in noninvasively measured left ventricular systolic function, while function improved in those who ceased or reduced their alcohol intake. One interesting finding was that ventricular performance improved even in patients who continued to consume a moderate amount of alcohol. This may be the consequence of a threshold effect, where toxicity is seen only above a certain level of alcohol consumption. Moderate alcohol consumption might also have other effects on the cardiovascular system beyond causing myocardial depression. It is important not to infer a change in muscle function from a change in ejection fraction, since the ejection-phase indices depend on the particular loading conditions of the ventricle.

While alcoholic cardiomyopathy has been recognized for many years, interest in other manifestations of alcoholic heart disease was stimulated by observations in the 1970s and 1980s regarding the apparent association between excessive alcohol consumption and the appearance of a variety of arrhythmias and sudden death. In one syndrome, termed the *holiday heart syndrome* because affected patients typically present with arrhythmia after binge drinking on a holiday, patients may have no other manifestations of end-organ damage and usually do not have left ventricular dysfunction or congestive heart failure. Several types of arrhythmias have been seen, most commonly atrial fibrillation but also atrial flutter and premature ventricular depolarizations (13). A study reported two decades ago used electrophysiologic testing to demonstrate that even modest doses of alcohol could produce rhythm disturbances in persons with a long-term history of alcohol abuse, most of whom had evidence of some form of heart disease (14). In the study by Nicolás and colleagues, 10 of 55 alcoholic men died during follow-up; all 10 men had continued to drink heavily (6). This finding highlights the potential importance of alcohol-related arrhythmias.

The study by Walsh and associates in this issue is intriguing because it did not show the expected association of heavier drinking with increased risk for congestive heart failure (7). Studying the well-established Framingham cohort, the investigators used a clinical scoring method to identify patients who developed congestive heart failure during follow-up. They found that the risk for congestive heart failure was not associated with heavier alcohol consumption; in fact, moderate alcohol use actually appeared to have a protective effect. What are we to make of these findings?

Several methodologic issues need to be considered before we discard our concept of alcohol-mediated heart damage. The first is the duration of alcohol use in these patients. Regan (10) and others have emphasized that alcoholic cardiomyopathy typically is seen after at least a decade of consistent consumption of at least 80 g of alcohol per day; the study by Nicolás and colleagues required a minimum of 10 years' consumption of at least 100 g/d (6). This information is not available in the study by Walsh and associates, and thus patients may not have had enough toxic exposure to cause heart failure during the study. In addition, the Walsh study did not include a direct measure of left ventricular function, such as echocardiography or nuclear techniques. Objective measures of cardiac performance usually are considered necessary to supplement clinical heart failure scores and reduce the false-positive rate (15, 16). We do not know how many patients actually had asymptomatic ventricular dysfunction that may become symptomatic at some point in the future. These issues notwithstanding, the Walsh study is well done and challenges some of our established principles. Whether the methodologic issues raised account for the results remains unclear. It should be emphasized that this study is not the only one to question the association of left ventricular systolic dysfunction and alcohol consumption. In a previous study, left ventricular function did not differ in 89 asymptomatic patients with chronic alcoholism compared with controls, although the alcoholic patients did have more evidence of left ventricular diastolic dysfunction (17).

The Walsh study further supports the concept that some degree of alcohol consumption may actually be protective and beneficial; similarly, the Nicolás study showed improvement in left ventricular function even with continued moderate alcohol consumption. Several epidemiologic studies have suggested a U-shaped mortality curve as a function of alcohol use, with moderate alcohol consumption associated with *reduced* mortality Perhaps most interesting is the so-called French paradox: In France, despite risk factors for coronary arter disease that are no lower and perhaps higher than usua (such as a diet high in saturated fats), persons have muc lower mortality rates for coronary heart disease than i most other European countries, a phenomenon that ha been attributed to the consumption of red wine (18, 19).

What to do with this kind of information is, o course, problematic. Are we really to encourage the us of moderate alcohol consumption, even though we ar aware of its multiple (potential) deleterious effects? think not, particularly given that while the cardiovascular mortality rate is significantly lower in France than i other European countries, the *overall* mortality rate i not (20). It has been suggested that part of the reaso for this dichotomy is a higher rate of alcohol-mediate noncardiovascular mortality (19). Given the widesprea use of alcoholic beverages in the western world, let u hope that the provocative studies reported in this issu will stir researchers to gain further understanding of th cardiovascular effects of alcohol.

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My two paternal uncles were both professional men. Wanda Landowska, the famous harpsichord player, knew them in Warsaw. She related to me some amusing stories about Uncle Stanislaw*, a doctor of medicine who was more famous as a raconteur than as a medical man. He caused discomfort to his patients by telling them that medicine was but an experimental science, and that the best he could do was to make sure that the pills and potions he prescribed would cause no harm; they were placebos calculated to make them feel good through sheer faith in their curative power. After listening to his reasoned discourse, a patient would go to another doctor."

*flourished circa 1890.

Nicolas Slonimsky
Perfect Pitch: A Life Story
New York: Oxford Univ Pr; 1988

Submitted by:
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Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.–*The Editor*

Emergency

Most mornings I enter the building that houses my office through the back door. And most mornings my mind is elsewhere. I am preoccupied with thoughts of the day ahead—things to accomplish, people to see, meetings to attend, a lecture to give, deadlines to meet.

But this morning, as I cross through the trauma center garage where I park my car, on the ground floor beneath the helipad, a man approaches me, disheveled, emaciated, his eyes a little wild, I notice as he nears me, walking straight toward me, quickly. I try to seem nonchalant, but I'm no longer preoccupied with anything but my immediate surroundings. I'm focused. The man has my attention.

When we are within touching distance he stops abruptly, holds out his hand (or is he reaching for me?), and mumbles something I don't quite catch. Directions maybe? People often ask for directions down here. I ask, "What'd you say?" "Can you spare some change?" he repeats, more slowly. And then, as if to assure me he's no panhandler, he thrusts his other arm forward to show me a soiled, makeshift bandage barely concealing a suppurating wound. "I got hurt. Been waitin' to get in. I need to get somethin' to eat," and he gestures toward the vending machines in the bare waiting room just behind us at the top of the ramp. I reach into my pocket and empty what change I have into his good hand and ask, "Will that help?" He replies, with gratitude, I think (his agitated expression didn't change), "If that's all you can spare." Whereupon he wheels around and retraces his steps jerkily toward the candy and chips machines.

I too turn and continue toward my office. All of a sudden I feel the softness of the leather attaché tucked under my bare, unspoiled arm. I look down and see my $200 shoes staring back at me. And the oil drippings all over the garage floor from the dilapidated vans and pickups that deliver their damaged human cargo to the ER. I become aware of an acrid odor in the humid morning air. And the cry of a siren approaching from afar, and the throbbing beat of the rotor blades of the Medivac helicopter landing on the roof, the air around me pulsating from the downward pressure. And in my mind's eye I see the big jail bus with the bars on the windows turn the corner toward the clinics. That must have happened as I got out of my car when the intersection was in my line of vision. But I don't remember seeing the bus then—only now.

As I pass out of the garage into the sunlight I see a morbidly obese woman, her legs swathed in elastic wrappings, leaning hard on her walker, lugging her great weight toward the hospital one labored step at a time. And I notice for the first time a sign that's surely been there for a couple of years announcing, "We care about your health. Our facilities and grounds are a smoke-free environment." On the benches beneath the sign the medically dispossessed gather, stealing a smoke, staring down and out, worrying, waiting.

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LETTERS

The Editors welcome submissions for possible publication in the Letters section. Authors of letters should: • Include no more than 300 words of text, three authors, and five references • Type with double-spacing • Send three copies of the letter, an authors' form (see Table of Contents for location) signed by all authors, a diskette containing the letter, and a cover letter describing any conflicts of interest related to the contents of the letter.

Letters commenting on an *Annals* article will be considered if they are received within 6 weeks of the time the article was published. Only some of the letters received can be published. Published letters are edited and may be shortened; tables and figures are included only selectively. Authors will be notified that the letter has been received. If the letter is selected for publication, the author will be notified about 3 weeks before the publication date. Unpublished letters cannot be returned.

Annals welcomes electronically submitted letters. The Internet address is www.acponline.org/shell-cgi/letter-article.pl.

Sponsorship, Authorship, and Accountability

TO THE EDITOR: Academic researchers must have complete freedom to participate in and approve all aspects of industry-sponsored clinical trials, including any publication resulting from such a trial. The Pharmaceutical Research and Manufacturers of America encourages all authors to abide by the new rules outlined in the editorial by the International Committee of Medical Journal Editors (1).

That having been said, the editorial has serious defects. Its biased tone slights the vital contributions of our industry to the clinical trial process. Throughout the editorial, the integrity of academic investigators is assumed, while the industry's integrity is constantly questioned. The editorial ignores the fact that the trial sponsors usually do most of the actual work in clinical trials. There are many well-respected, highly ethical, and experienced clinicians working for the industry who are not subject to pressures that affect most academicians, such as the need to obtain grants and secure tenure

Thus, while our industry supports the need to ensure the independence of researchers, the editorial is unnecessarily antagonistic, which weakens its impact. A more balanced approach would have recognized the essential roles that both industry and investigators play in developing safe and effective medicines for patients.

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Reference

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TO THE EDITOR: We represent seven of the largest global contract research organizations (CROs). We agree with the International Committee of Medical Journal Editors (ICMJE) (1) that all research must be conducted and reported objectively, dispassionately, and with the highest levels of scientific accuracy and integrity.

Rather than as stated in the ICMJE editorial, however, the perception of "head-to-head" competition between CROs and academic sites is erroneous and does not accurately portray the roles, objectives, and operations of CROs in the clinical research process. Contract research organizations work on a sponsor's behalf in a highly regulated environment (2) to implement and manage a clinical trial according to the study protocol. They provide research services that include consultation in study design; facilitation of the recruitment of investigators and study patients; assurance of patient protection, data integrity, and data analysis to maximize the quality of research; and, in particular, guidance through the complex regulatory environment. Contract research organizations do not sponsor clinical trials, do not own trial data, do not provide routine patient care, and do not participate in agreements concerning publication rights and responsibilities, which are negotiated between sponsors and investigators. The CRO's contractual obligation is to ensure the integrity of data and compliance with U.S. Food and Drug Administration and international regulations, not specific results. This enhances, not erodes, the quality and standards of clinical trials.

Today, most clinical research in the United States is conducted by physicians in group practice settings, who are directly involved in office-based patient care. The research environment is strengthened, not jeopardized, by the increased numbers of clinical researchers and the expansion of research settings. The increased participation of private-practice physicians broadens the populations from which study participants are drawn, creating a vital population of primary care patients to complement the tertiary care populations typical of academic medical centers. At the same time, according to the survey referenced in the editorial, major medical centers are consistently reporting double-digit growth in both National Institutes of Health– and industry-sponsored clinical grant revenue.

Both academic and community-based investigators participate in CRO-managed clinical investigations, and many participate in the development of study protocols. In CRO-managed studies, the investigator is neither our employee nor our customer but an integral partner in the research process. The breadth of our research spectrum encourages us to seek the best and brightest physician-scientists across all clinical disciplines.

We maintain that CROs contribute to high-standard clinical research by working in collaboration with—not competing against—clinical investigators at both academic medical centers and community-based clinics.

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Reference

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IN RESPONSE: Mr. Holmer (for the Pharmaceutical Research and Manufacturers of America) presents one pole in the debate over studies funded by industry and performed by academics. Academic investigators and industrial sponsors both contribute to the accrual of new medical knowledge. An appropriate balance is struck when a novel treatment can be tested in an environment in which all data are freely available to all investigators. When a report is prepared for publication, the primary goal must be the fair, honest, accurate, and complete dissemination of the accrued information. The system is best served when there is no attempt to present the study results in a more favorable light by selectively reporting the data.

The CRO Consortium argues that CROs have an auxiliary function in the performance of clinical trials and that CROs do not compete with academic investigators. We did not wish to diminish the role of CROs; these organizations provide substantial benefit with respect to the orderly accrual of complex clinical research data sets. However, CROs act as agents for the sponsor, not the investigator. When a sponsor does not want to deal with an investigator, the CRO may provide just enough separation to make such discrimination easy.

International Committee of Medical Journal Editors

Note: Part or all of this response may be published in other ICMJE journals.

Low-Dose Thiazide and Bone Density

TO THE EDITOR: LaCroix and colleagues (1), in a 3-year randomized, controlled trial, demonstrated that low-dose hydrochlorothiazide increased bone density in elderly normotensive men and women. They subsequently recommended considering hydrochlorothiazide in osteoporosis prevention programs. I believe this recommendation is too general and deserves further clarification.

The beneficial effect of hydrochlorothiazide on bone is probably related to its action on kidney tubules to promote calcium reabsorption. Urinary calcium excretion increases in postmenopausal women. This physiologic phenomenon, also known as postmenopausal renal calcium leak, has been attributed to reduced tubular reabsorption of calcium secondary to decreased estrogen effect on kidney tubules in the postmenopausal period (2). In the trial by LaCroix and colleagues, the greater effect of hydrochlorothiazide on bone density in women than in men is probably linked to postmenopausal calcium leak. The relationship between urinary calcium excretion and effect on bone density was not assessed in this study.

Calcium leak can be estimated by 24-hour urinary calcium excretion, and a normal reference range in postmenopausal women has been established (3). Estrogen therapy has been shown to decrease urinary calcium excretion in postmenopausal women (4). In addition, calcium supplementation may help restore serum calcium levels and prevent the development of secondary hyperparathyroidism and osteoporosis. The trial by LaCroix and colleagues excluded women taking estrogen, and mean total calcium intakes for both men and women were less than current recommendations (5).

Considering these facts, the clinical implications of this study may be summarized as follows. First, clinicians should consider the beneficial effect of hydrochlorothiazide on bone while deciding on a treatment plan for older adults with hypertension. Second, hydrochlorothiazide may be indicated in postmenopausal women with excessive degrees of renal calcium leak. Last, there is currently not enough evidence to recommend hydrochlorothiazide to normotensive elderly men or to women who have an adequate calcium intake and do not have significant calcium leak.

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5. NIH Consensus conference. Optimal calcium intake. NIH Consensus Development Panel on Optimal Calcium Intake. JAMA. 1994;272:1942-8. [PMID: 7990248]

IN RESPONSE: We agree with Dr. Kamel that reversal of renal calcium leak may be one mechanism whereby hydrochlorothiazide preserves bone density in older adults, a possibility noted in our discussion. We also noted that evidence supports other mechanisms as well.

In our trial, calcium deficiency did not explain the observed beneficial effects of thiazide. Although we did not provide calcium supplements, we did inform participants of their baseline calcium intake. Subsequently, at every visit, we assessed calcium intake and actively encouraged participants to maintain intakes of at least 1000 mg/d. As shown in the Figure, the mean total daily calcium intake during the study was 1600 mg/d among women in the placebo group compared with 1400 mg/d among women in the two hydrochlorothiazide groups. In men, the mean calcium intake was about 1200 mg/d in all three study groups during the 3-year follow-up. Therefore, the significant treatment effect seen with hydrochlorothiazide is over and above any effect of adequate calcium intake. On the basis of data from Dawson-Hughes and colleagues (1), the relatively stable levels of bone density in our placebo group might be attributed to adequate calcium intake. We are currently investigating the renal physiologic effects of thiazide in these participants. This analysis is complex, involving such factors as calcium, sodium, and protein intakes; urine sodium, phosphate, and creatinine levels; and serum levels of calcium, creatinine, and parathyroid hormone.

We agree that evidence from a fracture outcome trial is lacking as a basis for recommending hydrochlorothiazide for fracture prevention in healthy older adults. On the basis of available experimental and epidemiologic evidence, we continue to believe that low-dose thiazide could play a role in prevention of bone loss.

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Correction: Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection

In an article on adherence to protease inhibitor therapy and outcomes in HIV infection (1), the General Health Questionnaire score in Table 4 should be 6.8 ± 0.8 for patients with less than 95% adherence, and the P value for this variable should be 0.0014.

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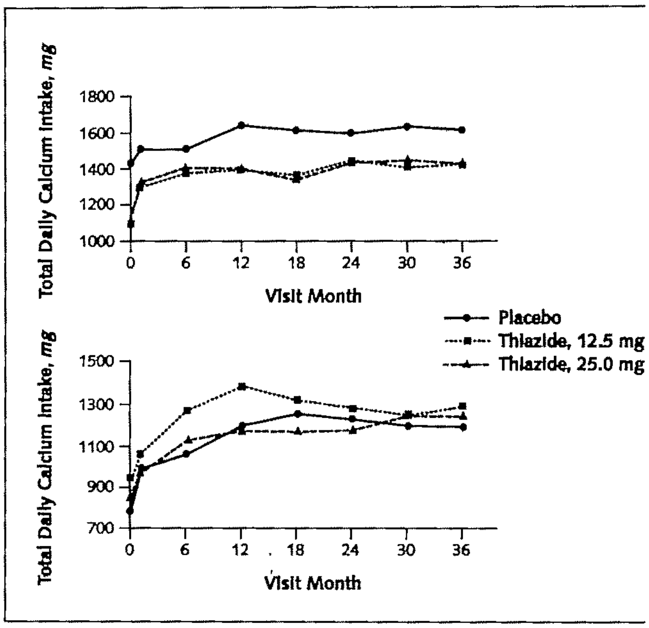
Figure. **Total calcium intake from diet plus supplements during 3 years of follow-up among 205 women (*top*) and 115 men (*bottom*), according to study group.**



Correction: Blood Flow to the Heart during the Menstrual Cycle

In a recent summary for patients (1) that accompanied the paper by Kawano and colleagues (2), the last sentence in the section "What did the researchers find?" should read "Ischemia was least frequent in the middle of the menstrual cycle (around the time of ovulation), when estrogen levels were *lowest* and the blood vessels were most likely to dilate."

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2. Kawano H, Motoyama T, Ohgushi M, Kugiyama K, Ogawa H, Yasue H. Menstrual cyclic variation of myocardial ischemia in premenopausal women with variant angina. Ann Intern Med. 2001;135:977-81. [PMID: 11730398]

The Landscape and Lexicon of Blinding in Randomized Trials

Blinding in medical research possesses a rich history spanning a couple of centuries (1). Most researchers and readers grasp its meaning. Unfortunately, beyond that general understanding lies confusion. In addition to terms such as "single blind" and "double blind" meaning different things to different people, some steadfastly refuse to use the term "blinding" and insist instead on the term "masking." Others confuse blinding with other methodologic precautions, such as concealment of allocation during the process of creating comparison groups. Still others consider that randomization is of little use unless accompanied by "double-blinding," thus revealing that they have not understood that these separate aspects of methodology address separate sources of bias.

A recent survey addressed whether the process historically termed "blinding" should be termed "masking" (2). The survey revealed a lack of accord on that question and inconsistencies concerning other blinding terminology. Although many resources address the lexicon of blinding, including clinical trial textbooks (3–5), clinical trial dictionaries (6, 7), and a recently released epidemiology dictionary (8), these sources do not entirely clear the lexicographic fog. Indeed, a recent study found that investigators, textbooks, and published articles all varied greatly in their interpretations of single-, double-, and triple-blinding (9). In other words, terminologic tangles abound with blinding. We delve into the landscape and lexicon of blinding in randomized trials in the hope of untangling some of that terminology.

SYNOPSIS OF THE HISTORY OF BLINDING

Scientists sometimes portray blinding as a recent methodologic achievement, but researchers have used blinding for more than 200 years. Lavoisier and Franklin introduced blinding in the late 18th century to test therapeutic claims made for Mesmerism—a therapy founded on the notion that magnetism had healing properties (1, 10). Toward the middle of the 19th century, many homeopaths used blinding in their "provings" and in comparisons of homeopathy with mainstream medicine (11). By the late 19th century, psychological researchers began to use blinding for traditional questions, more to minimize bias than to expose fraud (1). The beginning of the 20th century found some physiologists and pharmacologists, particularly in Germany, using blind assessment. That use became more frequent in Germany by the 1930s.

Researchers in Britain and the United States developed interest in blind assessment, but a different rationale motivated their interest. The rationale in Germany for blinding centered on the elimination of bias. In contrast, the interest in Britain and the United States initially centered on preventing attrition problems (1). Without blinding and a placebo intervention, recruiting and retaining participants for a no-intervention control group became daunting. "For Anglo-American clinical researchers, the initial adoption of a placebo sham in an experiment was an architectural device to create a viable and camouflaged concurrent no-treatment arm in a clinical trial" (1). Toward the end of the 1930s, British and U.S. researchers also began to acknowledge the benefits of blinding in avoiding bias.

The evolution of the randomized, controlled trial during the first half of the 20th century promoted greater use of blinding. Properly concealed random allocation to comparison groups abolished selection bias at entry to a trial, and clinical investigators began to appreciate fully the biases that could affect studies after participants had entered a trial. That realization transferred greater credibility to blinding arguments (1). We recommend Kaptchuk (1) for a historical account.

BACKGROUND

Blinding is intended to reduce bias in medical research. Although blinding is often associated in people's minds with randomized, controlled trials, it can be used in a variety of study designs to reduce observer biases (12). For example, investigators can assess outcome measures blinded to exposure status in nonrandomized cohort studies or exposure status blinded to case or control status in case–control studies. Indeed, when investigators first used blinding in the 18th century, they assessed the effects of Mesmerism in nonrandomized experiments (1, 10). Having noted this, however, we focus on blinding in the context of randomized comparisons of interventions.

Blinding is widely recognized as reducing differen-

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tial assessment of outcomes of interest (known as ascertainment bias, information bias, or observer bias), prompted by knowledge of the group assignment of individuals being observed (3–5). Blinding is less frequently recognized as also operationally improving compliance and retention of trial participants and reducing biased supplemental care or treatment (sometimes called co-intervention) (3, 5). We provide glimpses of the potential disadvantages of participants', investigators', and outcome assessors' knowing the intervention group to which the participants have been assigned. In many cases, the biases that result might well be subconscious, but they are biases nonetheless.

Possible Consequences of Participants' Knowing

Psychological effects could arise from participants' knowing that they have received a "promising" new treatment, a thoroughly tested standard treatment, an untested new treatment, or a "disappointing" standard treatment. In other words, how the treatment options are perceived may influence the way in which they are evaluated. Despite evidence suggesting that new treatments are as likely to be inferior as they are to be superior to standard treatments (13), we have the impression that participants generally assume that new treatments will be better than standard treatments. In any case, knowledge of the intervention received can affect the psychological or physical responses of the participants (3–5).

Furthermore, knowledge of the intervention could influence participants' cooperation. For example, if participants believe that they were assigned to what they perceive as an inferior intervention, they may not comply well with the regimen. Moreover, they may not adhere to follow-up procedures, leading to a potentially biased loss to follow-up.

Possible Consequences of Investigators' Knowing

We define investigators in an aggregate sense to include a broad trial team—for example, trial designers, participant enrollers, randomization executors, health care providers, intervention counselors, and routine-data collectors. Investigators particularly pertinent to blinding include health care providers (such as an attending physician or nurse) and intervention counselors (for example, someone delivering a behavioral prevention message) who interact with the participants throughout the trial. The inclinations of investigators for or against the interventions can be directly transferred to participants by their attitudes (14). Their inclinations may also be manifested in, for example, differential use of ancillary interventions of supplemental care or treatment (co-interventions). Of note, the implementer could also encourage or discourage continuation in the trial on the basis of knowledge of the intervention group assignment.

Possible Consequences of Outcome Assessors' Knowing

When they know the intervention group assignment of the participants whom they are assessing, outcome assessors with inclinations for or against any of the interventions being compared may make biased assessments. For example, if they believe the new intervention is superior, then they could register more generous responses to that intervention. Obviously, more subjective outcomes present greater opportunities for bias. Pain scores assessed by participants are a good example of a subjective outcome. Even some outcomes considered objective can be fraught with subjectivity—for example, pelvic inflammatory disease and myocardial infarction.

In general, blinding becomes less important to reduce observer bias as the outcomes become less subjective. "Hard" outcomes leave little room for bias. For example, knowledge of the intervention would have little effect on measuring a "hard" outcome, such as death (but still could influence the attributed cause of death). Of importance, even when participants and investigators have not been blinded, blinding of outcome assessors is often possible and advisable (12).

PLACEBOS AND BLINDING

Blinding frequently leads to the use of placebos. Placebos may or may not have effects mediated through psychological mechanisms, but they are administered to participants in a trial because they are otherwise "inactive." An "active placebo" is a placebo with properties that mimic the symptoms or side effects (for example, dry mouth, sweating) that might otherwise reveal the identity of the (pharmacologically) active test treatment. The effect, in practice, of using placebos is contentious (15), but the widespread view remains that placebos should be administered, whenever possible, to participants in control groups when assessing the effects of proposed new treatments for a condition for which no effective treatment already exists (3, 4). Placebos are generally used in trials of drugs, vaccines, and other medicinal interventions but can sometimes also be used in trials of procedures, such as ultrasonography, acupuncture, and, occasionally, surgery. For example, perhaps when placebo treatments are inappropriate, some closely analogous approach, such as placebo wound dressings, may suffice in a trial of laparoscopic versus open appendicectomy (16).

When an effective standard treatment exists, it is frequently used in the control group for comparison against a new treatment. Thus, investigators might compare two active treatment groups without a placebo group. Even then, however, investigators frequently attempt to achieve blinding by using the "double-dummy" method—in essence, two placebos (12, 17). For example, in comparing two agents, one in a blue capsule and the other in a red capsule, the investigators would prepare blue placebo capsules and red placebo capsules. Then both treatment groups would receive a blue and a red capsule, one active and one inactive.

TERMINOLOGY TANGLES

Double Definitions of "Double-Blinding"

Blinding (masking) describes a situation in which knowledge of intervention assignments is hidden from participants, investigators, or outcome assessors in a trial. The term "double-blind" denotes a trial in which the participants, investigators, and assessors all remain unaware of the intervention assignments throughout the trial. Given that three groups are kept ignorant, the term "double-blind" is sometimes misleading. In medical research, however, the same individual often is both investigator and assessor, so in that instance, the terminology accurately refers to two categories.

The term "single-blind" denotes a trial in which one of the three categories of individuals remains unaware of the intervention assignments throughout the trial. Typically, however, it connotes a trial in which the participant, not the investigator, remains ignorant (4). Moreover, a single-blind trial may confusingly refer to the participant and implementer both knowing the intervention but the assessor remaining unaware of it.

The terms "nonblind" and "triple-blind" also deserve attention. "Nonblinded" (open label) denotes trials in which all three categories of individuals know who has received which interventions throughout the trial. When investigators use the term "triple-blind," they usually mean a double-blind trial that also maintains a blind data analysis (3). Some investigators, however, denote trials as triple-blind if investigators and assessors are distinct people and both, as well as participants, remain unaware of assignments. Investigators rarely use the term "quadruple-blind," but some use it to denote blinding of participants, investigators, assessors, and data analysts (7).

Readers may note some fuzziness in our discussions of single-, double-, and triple-blinding. That fuzziness reflects true ambiguity. Indeed, universally accepted definitions have eluded the scientific community, and scanty reporting on blinding pervades the literature. Authors have frequently reported their study only as double-blind and not provided much further clarifying information (18–21). Of concern, a recent study (9) found that the term "double-blind" was interpreted differently among authors, readers, and "experts." A survey of physicians and a review of recent textbooks and reports revealed numerous interpretations of the designation "double-blind." For example, some thought it meant that the patients (participants) and clinicians (investigators) were blinded, whereas others thought that the patients and outcome assessors were blinded (9). In sum, investigators do not define "double-blinding" consistently, and to make matters worse, they frequently fail to report their definitions clearly in their articles.

Most important, we urge that authors explicitly state what steps were taken to keep whom blinded. If they choose to use terminology such as single-, double-, or triple-blinding in reporting randomized controlled trials, they should explicitly define those terms. When we use the term "double-blinding" in this article, we are referring to a situation in which steps have been taken to blind participants, investigators, and outcome assessors to group assignments.

"Blinding" or "Masking"

Some people use the term "masking" in place of "blinding." Similarly, "double-blinded" becomes "double-masked." For example, one prominent text uses blinding and double-blind (3), whereas another prominent text uses masked and double-masked (4). With that disparity, we are not surprised that researchers question and debate the proper terminology. Remarkably, few researchers have investigated the effect of terminology on trial participants or the meaning of terminology to investigators themselves (9).

"Masking" may have originated relatively recently as a euphemism for "blinding" in trials involving participants who have impaired vision. In those trials, "masking" may indeed be more appropriate because it may be less upsetting and offensive. It also would be less confusing in trials in which blindness is an outcome. In trials not addressing impaired vision, however, the term "blinding" does not seem to be upsetting or offensive to trial participants (2).

Both the process and the terminology of blinding, furthermore, appear to be well understood by most participants and investigators. That understanding evolved over two centuries of use (1). Blinding became ingrained in the principles of medical research. That blinding terminology seems to be universally recognized represents a lofty achievement for any term, let alone a methodologic term. Discarding a widely understood and instantly identifiable term would seem unwise, particularly in trials not addressing impaired vision, unless evidence to the contrary emerges.

In addition, blinding terminology conveys a strong bias-prevention message. Apparently, "blinding" terminology emerged when Benjamin Franklin and colleagues actually blindfolded participants to shield them from knowledge in their evaluations of the therapeutic claims made for Mesmerism (10). The visual imagery of blindfolding, a total covering of the eyes, conveys stronger bias prevention than masking, in which eye holes may permit extensive viewing. Moreover, the International Conference on Harmonization (ICH) guidance primarily uses "blinding" terminology (22). (The ICH is an intensive tripartite collaboration between regulatory authorities in Europe, Japan, and the United States to develop common guidelines for the design, execution, and the reporting of clinical trials.) The long history, pervasive general understanding, strong visual imagery, and adoption by the ICH lead us to suggest that "blinding" should remain the predominant terminology. With global electronic access to articles, if authors use "masking," we feel they risk the loss of comprehension in many parts of the world. Clearly, however, some investigators and editors prefer "masking" terminology (23).

"Blinding" and "Allocation Concealment"

The success of randomization depends on two interrelated processes (24–26). First, an unbiased allocation sequence must be generated, preferably by some random procedure. Second, strict implementation of that schedule must be secured through an assignment process that prevents foreknowledge of treatment assignment (24–26). That second strict implementation process, which we term "allocation concealment," is often confused with blinding. Allocation concealment prevents those who admit patients to a trial from knowing the upcoming assignments.

To judge from reports of controlled trials (25, 27, 28), the crucial importance of the allocation concealment process has not been widely recognized until recently (24, 29). Any notion of its importance seems to have been usurped under the rubric of "double-blinding." Moreover, one paper that gave rare recognition to the distinct process of "allocation concealment" termed it "randomization blinding," perhaps yielding further confusion (30).

"Allocation concealment" refers to a distinct process and should not be confused with blinding according to the terms in which we have described the latter. Allocation concealment seeks to prevent selection bias, protects the allocation sequence *before and until* assignment, and can *always* be successfully implemented regardless of the study topic (24, 25). In contrast, blinding seeks to prevent ascertainment bias, protects the sequence *after* allocation, and cannot always be implemented—for example, in trials comparing surgical with medical treatments. Thus, allocation concealment up to the point of assignment of the intervention and blinding after that point address different sources of bias and differ in their practicability. In light of those considerations, we introduced the term "allocation concealment" (24, 25) to describe the process used to prevent foreknowledge of intervention allocations before assignment. We exclusively reserve the term "blinding" for measures taken to conceal group identity after assignment.

"Double-Blinding" and "Randomization"

"Double-blinding" is intertwined with randomization. Apparently, double-blinding emerged as a concept more easily understood than randomization. With that understanding came confused terminology. One egregious confusion particularly annoys us. Our impression garnered over years of observation suggests that many investigators and readers delineate a randomized trial as high quality if it is "double-blind," as if double-blinding is the sine qua non of a randomized controlled trial. For example, a widely used scoring system for the quality of randomized trials accounts for double-blinding but not directly for allocation concealment (31). A randomized trial, however, can be methodologically sound in terms of controlling selection bias (proper randomization) and not be double-blind or, conversely, double-blind and not methodologically sound in terms of controlling selection bias. Although double-blinding reflects good methods, it should not be used as a surrogate marker of overall trial quality. As we discuss below, adequate allocation concealment actually appears the more important indicator. Moreover, many trials cannot be double-blinded. Those trials must be judged on merit and not on an inapplicable standard based on double-blinding.

DOES BLINDING PREVENT BIAS?

Although we feel that investigators, readers, and editors sometimes overestimate the importance of "double-blinding," we do not suggest that blinding is unimportant. Intuitively, blinding should reduce bias, particularly in estimating effects on some kinds of outcomes. More important, a systematic review of the empiric methodologic evidence supports that intuition (32).

Although not double-blinding appears to introduce bias, its average effect—exaggerating estimates by about 19% (32)—appears weaker than that of allocation concealment. Trials with inadequate or unclear allocation concealment have been shown to yield larger estimates of treatment effects compared with those that used adequate concealment (on average, 41% and 33%, respectively) (24), with commensurate results when the inadequate and unclear categories are lumped (29, 32). Double-blinding appears important in preventing bias but not as important as allocation concealment.

Blinding must succeed to reap its benefits. Investigators who use blinding can assess the success of the blinding by directly asking participants, investigators, or outcome assessors which intervention they think was administered. In principle, if blinding was successful, these individuals should not be able to do better than chance when guessing the intervention. In practice, adverse side effects may sometimes provide strong hints about the intervention. Furthermore, individuals may be reluctant to expose their unblinding efforts, if undertaken, by providing accurate responses to the queries—in other words, if they have deciphered group assignments, they might not be willing to incriminate themselves as having done so. To be sure, testing the success of blinding involves some difficulties in interpretation. Nevertheless, if investigators attempt to judge the success of their blinding, they should provide the results of those attempts. At the least, investigators need to report any failure of the blinding procedure, such as use of nonidentical placebo or active preparations.

SUMMARY

"Blinding" terminology rests on a long history, evokes widespread understanding, creates strong impressions, and pervades the international harmonization guidelines. We prefer "blinding" over "masking" terminology. The term "double-blinding" cannot be a surrogate marker for the methodologic quality of a randomized controlled trial. Each trial must be judged on its own merit, with blinding being just one component. Another, more important component—allocation concealment—should not be confused with blinding. A trial can use an adequate allocation concealment mechanism but use a totally inadequate blinding method.

Trial reports would benefit from authors' following the CONSORT guidelines (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) (33). They should eschew using only the single-, double-, triple-blinding terminology in favor of explicitly stating who was blinded and, to the extent possible, if blinding was successful. If they use terminology such as "double-blind," they should explicitly define it. Moreover, if the authors contend that trial participants, investigators, and outcome assessors were blinded, then the authors should describe, at a minimum, the mechanism (such as capsules, tablets) and the similarity of treatment characteristics (for example, appearance, taste, administration). Readers deserve information on those elements to judge the adequacy of blinding attempts. Moreover, better reporting might inspire better understanding.

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MEDICAL WRITINGS

BOOK NOTES

Structured abstracts of information on newly published books, computer programs, selected Web sites, and other material are provided in this portion of Medical Writings. "Order phone" numbers can be used to place orders directly with publishers.

Interpreting Electrocardiograms: Using Basic Principles and Vector Concepts

Hurst JW. 317 pages. New York: Marcel Dekker; 2001. $165.00. ISBN 0824705130. Order phone 212-696-9000.

Field of medicine: Electrocardiography.

Format: Hardcover book.

Audience: Clinicians and house officers in internal medicine who intend to sharpen their diagnostic accuracy in electrocardiographic interpretation.

Purpose: To provide and emphasize the vector concept as a basis for understanding electrocardiographic interpretation.

Content: The book has 7 parts. Part I describes elements of the learning process. Some would consider this topic sophomoric; however, when J. Willis Hurst—an outstanding teacher, clinician, and prolific cardiovascular author—deems this chapter important, others should listen. The succeeding parts of the book discuss interesting historical aspects of the electrocardiogram, the basic principles of electrocardiographic interpretation, the electrocardiogram as a clinical diagnostic tool, normal variations in the electrocardiogram, and specific and diagnostic electrocardiographic abnormalities.

Highlights: Hurst highlights the spatial vector approach to the understanding and interpretation of electrocardiograms. This approach, in which all letters applied to the electrocardiographic waves (P, QRS, ST, T, and U) are used as diagnostic vectors, simplifies and improves the diagnostic accuracy of the electrocardiogram.

Limitations: There is no chapter on arrhythmias; the author states that this omission was intentional. Several figures (for example, figures 10-1 and 10-2) should be enlarged or simplified to enhance readability. Figure 27-1 has electrocardiographic features consistent with hypocalcemia in addition to hyperkalemia, and although these are characteristics of chronic renal failure, the legend describes only hyperkalemia. In chapter 7, the normal ST segment is described as "flat and isoelectric." However, in leads that reflect the electrical potentials of the epicardial surface of the left ventricle, the normal ST segment is flat and isoelectric for only 60 to 80 milliseconds after takeoff from the QRS but then rises slightly before joining the asymmetric proximal limb of an upright T wave. A continued flat isoelectric ST segment would be the first sign of abnormality.

Related readings: Of the many textbooks on electrocardiography, few stress the spatial vector concept as do Hurst or Grant. The 14 seminal papers published by Myers and colleagues from 1948 to 1951 on the correlation of electrocardiographic and pathologic findings in infarctions involving various areas of the myocardium are useful for anyone interpreting electrocardiograms.

Reviewer: Louis Lemberg, MD, Division of Cardiology, University of Miami School of Medicine, Miami, Florida.

Emerging Infections 5

Scheld WM, Craig WA, Hughes JM, eds. 242 pages. Washington DC: ASM Pr; 2001. $79.95. ISBN 1555812163. Order phone 800-546-2416.

Field of medicine: Infectious diseases, microbiology, and public health.

Format: Softcover book.

Audience: Infectious diseases physicians, medical microbiologists, hospital epidemiologists, public health officials, and policymakers. Specific chapters are likely to have broader appeal. For example, the chapter on waterborne diseases and hemodialysis may interest nephrologists; the chapter on enterovirus 71 may interest pediatricians and neurologists; the chapter on *Mycoplasma pneumoniae* is likely to interest most internists; and the chapters on West Nile virus, bioterrorism, and plague and anthrax are likely to interest emergency medicine physicians, primary care physicians, and many in the general public.

Purpose: To serve as a source of current information for persons coping with infectious diseases in the new millennium.

Content: Infections due to enterovirus 71 in Taiwan, West Nile Virus in New York City, *Coxiella burnetii* (Q fever), *M. pneumoniae*, community-onset oxacillin-resistant *Staphylococcus aureus*, small-colony variant *S. aureus*, *Clostridium difficile*, *M. ulcerans* (Buruli ulcer disease), *Babesia* species, and *Entamoeba histolytica*. The book also covers the diversity of *Borrelia* species and their relationship to tick vectors; waterborne pathogens in hemodialysis; bioterrorism; and anthrax and plague in bioterrorism.

Highlights: The topics were selected because recent findings have changed our understanding. The authors are widely recognized authorities; the references are thorough and extensive. The prescient admonitions of Osterholm and Inglesby in their chapters on bioterrorism were chilling to read.

Limitations: The photographs of filtration canisters (chapter 8) and of test tubes and culture dishes (chapter 9) seem superfluous.

Related reading: Textbooks of infectious diseases provide a more balanced discussion of several of the topics in the classic format of epidemiology, pathophysiology, clinical manifestations, and treatment. However, textbooks are not as current, and can even be misleading, because recent findings have changed our understanding of the topics covered in this book. Perhaps the best comparable source of information is *Journal of Emerging Infections*, the full text of which is available at www.cdc.gov/ncidod/eid/. Compared to most journal articles, however, *Emerging Infections 5* treats the topics more thoroughly, with a broader perspective and more references.

Reviewer: Harrison G. Weed, MD, Division of General Internal Medicine, The Ohio State University College of Medicine, Columbus, Ohio.

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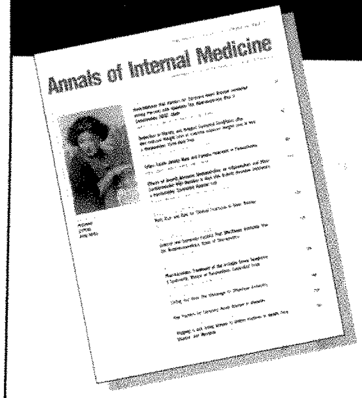

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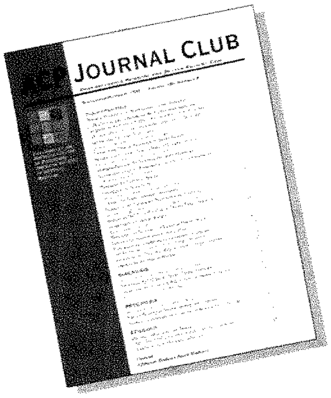

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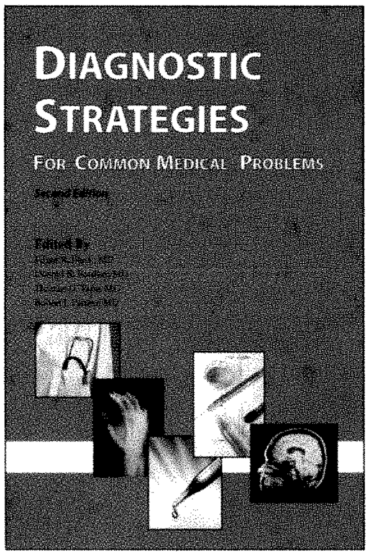
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A C P

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A 45-year-old woman presents with weight loss of approximately 9 kg (20 lb) over the past 12 months. She has been aware of no change in appetite. She eats three meals daily and snacks most evenings. Her activity has similarly been unchanged. She exercises by walking 2 to 3 miles three or four times weekly. She takes no medication and reports no alcohol or drug use. Review of systems reveals a 1- to 1.5-year history of a pruritic rash on the trunk and extremities. She reports occasional vague abdominal pain and bloating, which subside spontaneously in a few hours, and notes the passage of flatus. She has no food intolerance, difficulty swallowing, sweating, tremor, constipation, diarrhea, or arthritis. She has normal, regular menstrual periods and has two to three stools per day, with no recent change.

The patient is 175 cm (69 in) tall and weighs 50 kg (110 lb). Blood pressure is 115/70 mm Hg, pulse is 96/min, and temperature is 36.9 °C (98.4 °F). The skin shows a truncal and proximal extremity rash consisting of grouped vesicles on an erythematous base. There is also evidence of excoriation. The remainder of the physical examination, including pelvic and rectal examination, is otherwise normal, and stool is negative for occult blood. The neurologic examination is normal.

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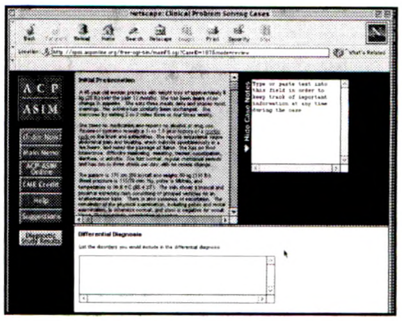

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R.J. Green, J.P. Metlay, K. Propert, P.J. Catalano, J.S. Macdonald, R.J. Mayer, and D.G. Haller

The incidence of second primary colorectal cancer after treatment for localized colon cancer remains high despite intensive surveillance strategies.

Change in Lung Function and Morbidity from Chronic Obstructive Pulmonary Disease in α_1-Antitrypsin *MZ* Heterozygotes: A Longitudinal Study of the General Population 270

M. Dahl, A. Tybjærg-Hansen, P. Lange, J. Vestbo, and B.G. Nordestgaard

A deteriorating effect of severe α_1-antitrypsin deficiency (*ZZ* genotype) on lung function is well known, whereas the role of intermediate deficiency (*MZ* genotype) remains uncertain. This study found that *MZ* heterozygotes had a slightly greater rate of decrease in FEV_1 and were modestly over-represented among persons with airway obstruction and chronic obstructive pulmonary disease (COPD). In the population at large, *MZ* heterozygosity may account for a fraction of COPD cases—on the order of 2%, similar to the percentage of persons with COPD who have the severe but rare *ZZ* genotype.

The Stool Antigen Test for Detection of *Helicobacter pylori* after Eradication Therapy 280

D. Vaira, N. Vakil, M. Menegatti, B. van't Hoff, C. Ricci, L. Gatta, G. Gasbarrini, M. Quina, J.M. Pajares García, A. van der Ende, R. van der Hulst, M. Anti, C. Duarte, J.P. Gisbert, M. Miglioli, and G. Tytgat

A positive result on the stool antigen test 7 days after completion of therapy identifies patients in whom eradication of *Helicobacter pylori* was unsuccessful.

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Surprisingly Small Effect of Antiviral Treatment in Patients with Hepatitis C 288

Y. Falck-Ytter, H. Kale, K.D. Mullen, S.A. Sarbah, L. Sorescu, and A.J. McCullough

Most patients with hepatitis C virus infection are not candidates for interferon-based therapies; alternative interventions should be sought for these patients.

UPDATE

Update in Psychiatry 293

R.K. Schneider and J.L. Levenson

This Update is the first Update in Psychiatry presented at an Annual Session of the American College of Physicians–American Society of Internal Medicine. The authors cover the following topics: mood disorders, anxiety disorders, geropsychiatry, and new therapeutics.

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A Current Perspective of Suicide and Attempted Suicide 302

J.J. Mann

Suicide is generally a complication of a psychiatric disorder, but it requires additional risk factors because most psychiatric patients never attempt suicide. This review includes a hypothesized stress–diathesis model, which has implications for detection of high-risk patients and treatment interventions, and discusses promising treatment approaches.

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Legal, Financial, and Public Health Consequences of HIV Contamination of Blood and Blood Products in the 1980s and 1990s 312

P.D. Weinberg, J. Hounshell, L.A. Sherman, J. Godwin, S. Ali, C. Tomori, and C.L. Bennett

This paper summarizes the current status of concerns about the safety of the blood supply in developed countries, where viral transmission from contaminated blood or blood products is extremely rare, and in developing countries, where up to 10% of HIV infections result from transfusion of blood or blood products.

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Future Directions in the Study and Management of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency 320

D.P. Merke, S.R. Bornstein, N.A. Avila, and G.P. Chrousos

In the past 50 years, since the discovery of cortisone therapy as an effective treatment for congenital adrenal hyperplasia, many advances have been made in the study and management of 21-hydroxylase deficiency. The discovery of the 21-hydroxylase gene was followed by the discovery of the 21-hydroxylase–deficient mouse, which has provided a

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useful model for testing new treatments. As our knowledge of this disease expands, new therapies are being developed and tested in both humans and animals.

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Second Primary Colorectal Cancer: The Consequence of Management Failure at Several Potential Levels 335
P.J. Limburg and D.A. Ahlquist

Although the study by Green and colleagues in this issue chronicles a disturbingly high rate of second primary colorectal cancer in patients undergoing surveillance in an adjuvant chemotherapy trial, the junctures at which corrective measures are most needed cannot be precisely determined. For now, adherence to the existing consensus guidelines for postoperative surveillance seems warranted until convincing evidence supports alternative strategies.

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Annals of Internal Medicine

Surveillance for Second Primary Colorectal Cancer after Adjuvant Chemotherapy: An Analysis of Intergroup 0089

Robert J. Green, MD, MSCE; Joshua P. Metlay, MD, PhD; Kathleen Propert, ScD; Paul J. Catalano, ScD; John S. Macdonald, MD; Robert J. Mayer, MD; and Daniel G. Haller, MD

Background: **The incidence of second primary colorectal cancer in patients with a history of colon cancer, compared with patients with a history of adenomatous polyps, is unknown. It is unclear whether guidelines for colonoscopy screening in patients with polyps are appropriate for patients with previous colon cancer.**

Objective: **To determine the incidence of second primary colorectal cancer after treatment for localized colon cancer and to compare this incidence with that of first primary colorectal cancer in both the general population and high-risk patients.**

Design: **Historical cohort study.**

Setting: **An international, multi-institutional trial of adjuvant 5-fluorouracil–based chemotherapy for localized colon cancer.**

Patients: **3278 patients with resected stage II and stage III colon cancer.**

Measurements: **Occurrence of endoscopic or radiologic colon surveillance and incidence of second primary colorectal cancer.**

Results: **Forty-two cases of second primary invasive colon cancer were found over 15 345 person-years of follow-up, yielding an incidence rate of 274 per 100 000 person-years (95% CI, 196 to 369 per 100 000 person-years) and a cumulative incidence of 1.5% (CI, 1.1% to 2.0%) at 5 years. This rate was compared with rates of first colon cancer in two reference groups: the general population and patients who had undergone frequent colonoscopy and polypectomy because of a history of adenomatous polyps; standardized incidence ratios were 1.6 (CI, 1.2 to 2.2) and 6.8 (CI, 2.7 to 22.0), respectively.**

Conclusion: **The incidence of second primary colorectal cancer remains high despite intensive surveillance strategies.**

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Colorectal cancer is a major public health problem, with more than 130 000 new cases thought to have occurred in the United States in 2001. Patients who have had colon cancer are at risk for second primary colon cancer, but the extent of this risk is unclear. The incidence and rate of development of second primary tumors have implications for appropriate surveillance of the colon after diagnosis of colorectal cancer.

After first primary colon cancer is diagnosed, resection with curative intent is possible in approximately 75% of patients because the disease is limited to the bowel or to regional lymph nodes. The standard of care for patients with stage II or stage III disease is surgical resection, followed by adjuvant therapy for stage III disease. After surgery and adjuvant chemotherapy, patients frequently undergo some form of surveillance. Computed tomography of the abdomen, chest radiography, and measurement of carcinoembryonic antigen have been used to detect distant metastatic disease, although no convincing data show that these tests are cost-effective or improve survival (1). Colonoscopy or barium enema combined with flexible sigmoidoscopy has been used to survey for second primary colorectal cancer.

Surveillance for second primary colorectal cancer serves two purposes: removal of premalignant polyps and early detection of malignancy. Most colorectal cancer is the product of slow, orderly progression from normal cells to malignancy. Surveillance with endoscopy and polypectomy has been shown to prevent colon cancer (2, 3). The most convincing data for this intervention come from the National Polyp Study, which found that in patients with adenomatous polyps, colonoscopic surveillance significantly decreased the incidence of colorectal carcinoma (3). The National Polyp Study also examined the question of how frequently to perform colonoscopic surveillance by comparing two surveillance strategies in patients who had recently had adenomas removed by colonoscopy (4). The study showed that repeated colonoscopy 3 years after colonoscopy and polypectomy in patients with adenomatous polyps was equivalent to more frequent surveillance. The authors conceded, however, that more frequent follow-up colonoscopy may be needed in patients with a history of colorectal cancer because they may have different biological characteristics and natural history.

Current guidelines for surveillance of patients with a

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Context

Patients who have had colorectal cancer can develop second primary colorectal cancer.

The American Cancer Society recommends that surveillance colonoscopy be performed 1 year after surgery, then every 3 to 5 years if results are negative. This surveillance strategy is unproven.

Contribution

This study documented an incidence rate of 274 cases of second primary colon cancer per 100 000 person-years after surgery with curative intent and 5-fluorouracil–based chemotherapy.

The incidence of second cancer was higher than the incidence of first colorectal cancer in the general population, despite surveillance.

Cautions

This study suggests that surveillance may need to be more vigilant than currently recommended.

However, more data are needed to decide how often to do surveillance colonoscopy.

–The Editors

history of colon cancer are at least partially based on data from the National Polyp Study. The American Gastroenterological Association and the American Cancer Society recommend complete examination of the colon within 1 year of resection; if findings on this or on complete preoperative examination are normal, examination should be repeated in 3 years and then, if findings are again normal, every 5 years (5). In addition to finding new second primary tumors, surveillance within 1 year of colon cancer surgery may detect previously undetected polyps or synchronous tumors. Recent recommendations from the American Society of Clinical Oncology call for perioperative colonoscopy followed by colonoscopy every 3 to 5 years (1). However, deciding whether to extrapolate surveillance recommendations for patients with polyps to patients with a history of colon cancer requires a better understanding of the absolute and relative risk for second colorectal cancer in such patients.

In the general population, the best estimates of the risk ratio for second primary colorectal cancer compared with first primary colorectal cancer have ranged from 1.5 to 3.0 (6, 7). The studies that have addressed this issue have had several deficiencies: incomplete follow-up, incomplete reporting of new cases, reporting of cumulative incidence rates (which do not consider length of follow-up), unknown surveillance practices in the study sample, arbitrary time cutoffs to distinguish new metachronous primary cancer from missed synchronous cancer, and heterogeneous patient samples (6–11). Thus, we do not know enough about the incidence of second primary colorectal cancer in patients with a history of colon cancer to devise optimal surveillance strategies. The purpose of our study was to estimate the incidence of second primary colon cancer in patients with a history of high-risk stage II or stage III colon cancer and to compare this incidence with that of first primary colon cancer in the general population and the National Polyp Study.

METHODS

Patients

Our study is a historical cohort analysis of patients who entered a trial of adjuvant therapy after surgery for colon cancer. This trial was designated Intergroup 0089 by the U.S. National Cancer Institute (12) and was approved by the Institutional Review Board of the University of Pennsylvania, Philadelphia, Pennsylvania. Patients with high-risk stage II or stage III cancer were randomly assigned to one of four 5-fluorouracil–based treatments. Patients were enrolled at 683 institutions, 73% of which were community-based medical centers. Surveillance guidelines for patients in the study included mandatory surveillance of the entire colon with colonoscopy or barium enema and flexible sigmoidoscopy at diagnosis, within 6 months of surgery, at 12 months, at 18 months, and then annually. At the discretion of each patient's physician, surveillance could be done less frequently (every 18 to 24 months after the 6-month surveillance).

Data Collection

Patients were required to visit the treating oncologist at least every 3 months during the first year of the study and then every 6 months for 4 years. After 5 years, follow-up materials were collected annually until death.

At each visit, data forms that included information on surveillance and documentation of second primary colorectal cancer were completed. Data on the diagnostic procedures used to diagnose the original colon cancer and on whether the entire colon was visualized at diagnosis were not always available, since these were not primary objectives of the protocol. Original data collection and statistical analysis were done by the Eastern Cooperative Oncology Group.

Reference Groups

We compared the observed incidence rate of second primary colorectal cancer in Intergroup 0089 with the rates of first primary colorectal cancer expected in two reference groups. The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute monitors the incidence of colorectal cancer in 10 statewide registries (13). These data are routinely used as a surrogate for the average risk for colorectal cancer throughout the United States. We used age-, sex-, and ethnicity-specific rates for calendar years 1989 to 1993 since this period corresponded to the time during which patients were enrolled in Intergroup 0089.

The National Polyp Study was a prospective study of 1418 patients who were referred for colonoscopy, during which one or more adenomas of the colon or rectum were removed (3, 4). The patients subsequently underwent periodic colonoscopy (randomly assigned to either years 1 and 3 or year 3 only) during an average follow-up of 5.9 years, and the incidence of colorectal cancer was ascertained. The incidence rate of colorectal cancer was compared with rates in three reference groups: two populations of patients with adenomatous polyps who did not have all polyps removed, and the SEER program. Five cases of invasive colorectal cancer were detected in a total of 8401 person-years of follow-up. The National Polyp Study found that colonoscopy with polypectomy decreased the incidence of colon cancer by approximately 90% compared with the other populations of high-risk patients and by 76% compared with the SEER population.

Statistical Analysis

In Intergroup 0089, the number of person-years at risk was calculated for each patient from the time of study entry until death, diagnosis of second primary colon cancer, or the last known time at which the patient was alive. Median time to second cancer and survival plots were calculated by using the Kaplan–Meier method. Incidence rates were defined as the total number of events divided by the total person-years of follow-up; 95% CIs were calculated by assuming a Poisson distribution.

Our study primarily analyzed the diagnosis of second primary colorectal cancer. We established criteria to distinguish second primary cancer from an anastomotic recurrence or metastases. A tumor was classified as a second primary tumor if it was pathologically described as arising from a preexisting polyp or was found at a site distant from the original primary tumor (not at the site of the anastomosis), without evidence of penetration from the serosa of the bowel. Only tumors discovered after the original resection were considered second primary tumors, and only invasive cancer was included. In situ tumors were excluded because they were not included in either of our comparison groups and because, given the lack of potential for metastatic spread, they are of less clinical relevance. In our primary analysis, we did not specify a minimum time interval between treatment of the original primary tumor and detection of a second primary tumor. However, in a secondary analysis, we excluded all person-years and second cases of cancer that occurred within the first 2 years of follow-up in order to address the possibility that some tumors were synchronous and not metachronous.

To compare the rate of second primary colorectal cancer in Intergroup 0089 with the rate of first primary cancer in the general population, we calculated the standardized incidence ratio for colorectal cancer in Intergroup 0089 compared with SEER data (14). The standardized incidence ratio is the ratio of observed to expected number of cases. Person-years at risk in Intergroup 0089 were stratified according to age, sex, and ethnicity. Rates of colorectal cancer in SEER that corresponded to each stratum were multiplied by the total number of person-years in each stratum to yield an expected number of cases. The expected numbers of cases were then summed to yield the total number of expected cases based on SEER rates. Exact 95% CIs were calculated by assuming a Poisson distribution for the observed number of cases of colon cancer in Intergroup 0089.

To compare the rate of second primary colorectal

Table 1. **Characteristics of Study Patients**

Characteristic	Value
Median age ± SD (range), y	63.9 ± 11 (15–87)
Sex, *n (%)*	
Male	1800 (55)
Female	1478 (45)
Location of primary tumor, *n (%)*	
Right colon	1567 (49)
Left colon*	1612 (51)
Stage; *n (%)*	
II	650 (20)
III	2628 (30)
Survival status, *n (%)*	
Alive	2011 (51)
Dead	1259 (39)
Ethnicity, *n (%)*	
White	2776 (85)
Black	318 (10)
Other	158 (5)

* Includes tumors coded in original database as located in "splenic flexure," "left colon," or "sigmoid colon."

cancer in Intergroup 0089 with the National Polyp Study, we calculated a ratio of two standardized incidence ratios: the standardized incidence ratios of Intergroup 0089 compared with SEER and the National Polyp Study compared with SEER. This ratio approximates the standardized incidence ratio of Intergroup 0089 to the National Polyp Study. The validity of this estimation, which has been used in previous studies (3), is contingent on homogeneity across strata of the ratios of rates in our study compared with the National Polyp Study and in our study compared with SEER (15), both of which we believe to be sound. Exact 95% CIs were calculated as described by Breslow and Day (14). To calculate standardized incidence ratios using only second primary colorectal cancer that occurred after 2 years of follow-up, we excluded all person-years and second primary colorectal cancer that occurred in the first 2 years after enrollment in Intergroup 0089 and repeated the calculations described earlier.

To determine the interval between surveillance and the diagnosis of second primary colorectal cancer, we performed two separate but complementary analyses. First, we looked only at the 18 patients who developed second primary colorectal cancer after the first 2 years of follow-up and measured the time since their most recent previous surveillance. Second, we looked at the 19 patients who had normal results on surveillance within 1 year of their original diagnosis and calculated the median time between this surveillance and the diagnosis of second primary colorectal cancer. All statistical analyses were performed with Stata 5.0 for Windows (Stata Corp., College Station, Texas).

Role of the Funding Source

The National Cancer Institute funded Intergroup 0089 but had no direct role in our study other than the participation of Dr. Catalano.

RESULTS

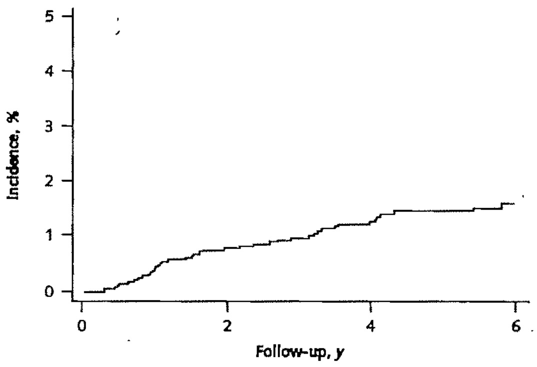
Patient Sample

After 10 October 1989, 3278 eligible patients with stage II or III colon cancer were enrolled in the study. Fifty-five percent of patients were men, and the median age was 63.9 years (Table 1). Eighty-five percent of patients were white. Median follow-up among patients still alive was 7.1 years, and 63% of patients had been followed for at least 5 years. Five percent of patients were lost to follow-up, and 39% of patients died during follow-up. Median survival was 9.4 years.

Second Primary Colorectal Cancer

Forty-two patients developed second primary colon cancer after an original diagnosis of primary colon cancer and adjuvant chemotherapy. Among these patients, the median age was 66 years (range, 28 to 81 years), 29 (69%) were men, and 37 (88%) were white. Twenty-

Figure 1. **Cumulative incidence of second primary colon cancer in Intergroup 0089.**



Year	0	1	2	3	4	5	6
Patients remaining, *n*	3278	3082	2758	2444	2209	1825	1042

Table 2. **Standardized Incidence Ratios Comparing Incidence of Second Primary Colorectal Cancer in Intergroup 0089 with Incidence of First Primary Colorectal Cancer in Two Reference Populations***

Time Frame	Cases of Colorectal Cancer Observed in Intergroup 0089	Cases of Colorectal Cancer Expected		Standardized Incidence Ratio (95% CI)	
		SEER	NPS†	SEER‡	NPS§
	← n →				
All years	42	26	–	1.6 (1.2–2.2)	6.8 (2.7–22.0)
First 2 years excluded	18	15	–	1.2 (0.7–1.8)	5.0 (1.8–17.4)

* NPS = National Polyp Study (3, 4); SEER = Surveillance, Epidemiology, and End Results Program (13).
† Expected number of cases cannot be calculated since a ratio of standardized incidence ratios was used as an estimate.
‡ Calculated as number of observed cases/number of expected cases.
§ Estimated by ratio of standardized incidence ratio for Intergroup 0089/SEER to standardized incidence ratio for NPS/SEER.

three cases of second primary cancer (55%) were stage I or stage II, 10 (24%) were stage III, and 9 were of undetermined stage (21%). Fourteen patients with second primary colon cancer (33%) died during the study period.

Incidence Rates

The 42 second cases of primary colon cancer developed over a total of 15 345 person-years of follow-up. This yields an incidence rate of 274 cases per 100 000 person-years (95% CI, 196 to 369 cases per 100 000 person-years) and a cumulative incidence of 1.5% (CI, 1.1% to 2.0%) at 5 years (**Figure 1**). The median time from the original diagnosis of colon cancer to diagnosis of second primary colon cancer was 18.4 months (range, 3.4 to 70.1 months). Eighteen cases (43%) occurred after more than 2 years.

Standardized Incidence Ratios

The incidence rate in Intergroup 0089 was compared with rates from the SEER program and from the National Polyp Study (**Table 2**). The standardized incidence ratio compared with the SEER program was 1.6 (CI, 1.2 to 2.2), and the standardized incidence ratio (as estimated by a rate ratio) compared with the National Polyp Study was 6.8 (CI, 2.7 to 22.0). When the first 2 years of follow-up in our study sample were excluded, the standardized incidence ratio was 1.2 (CI, 0.7 to 1.8) compared with SEER and 5.0 (CI, 1.8 to 17.4) compared with the National Polyp Study.

Surveillance

The surveillance histories of all 42 patients who developed second primary colon cancer are presented in **Figure 2**. Data from surveillance performed at the time of diagnosis of first primary cancer and before enrollment in the study were not reliably available. Most surveillance procedures were colonoscopies. In all patients except four, the most recent surveillance procedure before the discovery of second primary cancer was colonoscopy and not flexible sigmoidoscopy or barium enema.

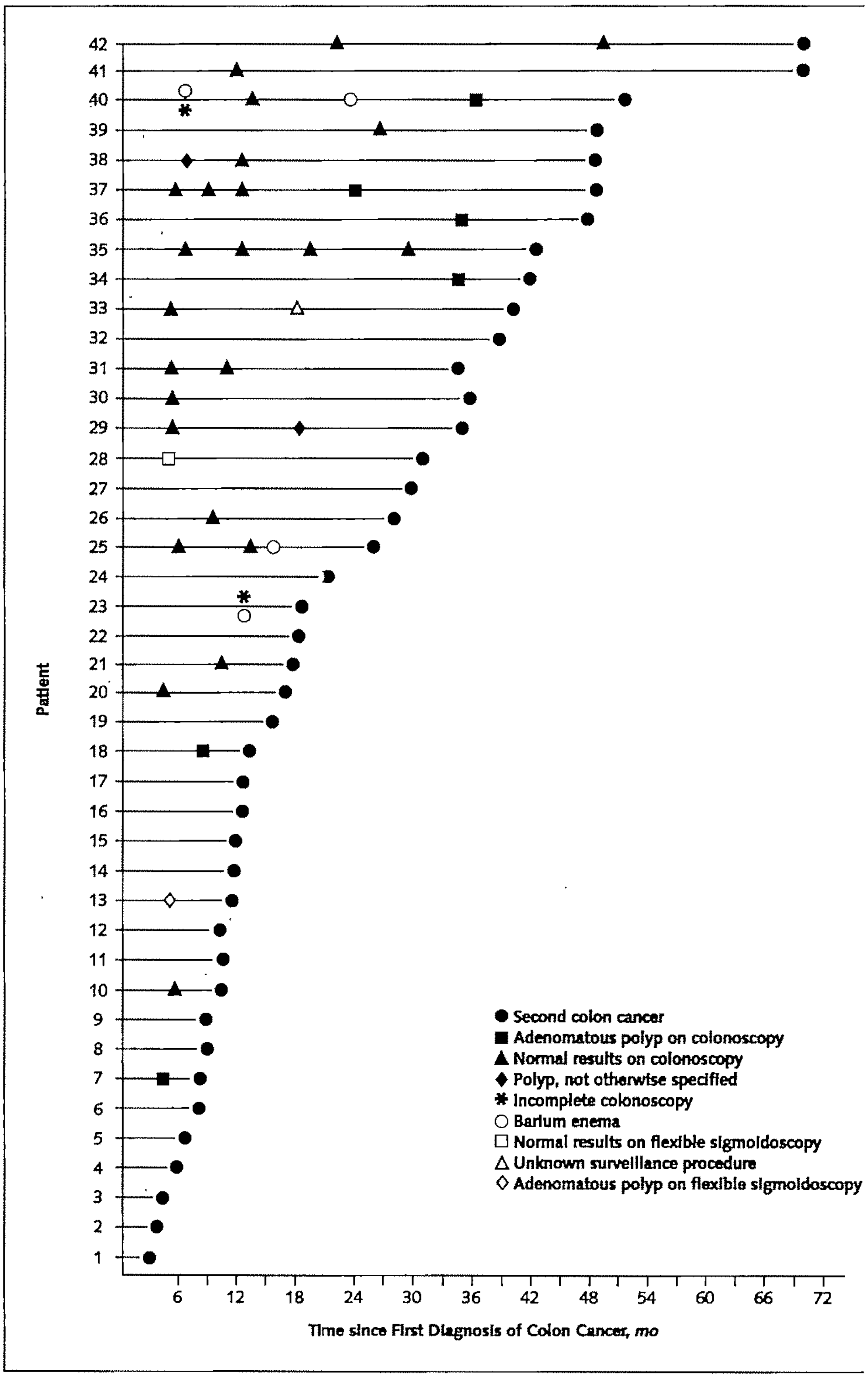
Nineteen of the 42 patients who developed second primary colorectal cancer had normal results on a surveillance procedure within 1 year after their original diagnosis (in effect, "clearing" the colon). The remaining 23 patients either did not have a surveillance procedure within the first year or had cancer diagnosed at the time of the first surveillance. The median time to diagnosis of a second primary tumor after the first surveillance procedure was 25.8 months (range, 4.9 to 57.5 months).

Eighteen patients developed second primary colorectal cancer after the first 2 years of follow-up. In these patients, the median time to the most recent previous surveillance procedure was 21 months (range, 7 to 58 months). Because many guidelines call for an interval of 3 years between colonoscopies for patients with a history of colon cancer, we also determined the percentage of these 18 patients who had a surveillance procedure within 3 years of diagnosis; 14 (78% [CI, 52% to 94%]) had had such a procedure.

DISCUSSION

Our study provides at least three important pieces of information. First, we found that the incidence of second primary colorectal cancer in a homogeneous cohort of intensively surveyed patients with an immediate history of stage II or stage III colon cancer was 1.5% (CI, 1.1% to 2.0%) at 5 years. Second, we have shown

Figure 2. **Second primary colorectal cancer and preceding surveillance.**



that despite protocol recommendations for rigorous surveillance, the incidence rate was higher in this population than in the general population and 6.8 times higher than in the National Polyp Study. Third, second primary colorectal cancer was diagnosed within a relatively short period after patients' most recent previous colonic surveillance. Our study provides important information regarding the incidence and latency period of this disease; however, we have not shown that current surveillance strategies are inadequate or that more intensive surveillance would result in decreased morbidity or mortality or would be cost-effective.

Our standardized incidence ratio compared with the SEER project was only 1.6 when we included all years of follow-up. However, the rate of second primary colorectal cancer in our study is not trivial. In fact, the 5-year cumulative incidence of 1.5% is almost identical to the 1.7% 5-year risk for breast cancer that was required for entry into the National Surgical Adjuvant Breast and Bowel Project P-1 Study (16), which used potentially harmful pharmacologic therapy to decrease breast cancer incidence. Furthermore, our incidence rate remained high when compared with the National Polyp Study, even after exclusion of second primary colon cancer found in the first 2 years of follow-up. Surveillance rates in patients who developed second primary colon cancer, while lower than had been recommended, were compatible with those in the National Polyp Study and those recommended by the American Gastroenterological Association, the American Cancer Society, and the American Society of Clinical Oncology. Therefore, rates of second primary colon cancer in Intergroup 0089 might have been expected to be similar to, not almost sevenfold greater than, rates of primary colon cancer in the National Polyp Study.

We believe that there may be at least two reasons for the increased rate of second primary colorectal cancer in Intergroup 0089. First, patients with a history of colon cancer may differ biologically from patients with adenomatous polyps and are therefore at higher risk for colorectal cancer. Second, surveillance in our community-based study (including whether patients had their entire colons visualized at the time of their original diagnosis) may not have been as accurate as that in the National Polyp Study. The primary intervention in the National Polyp Study was colonoscopy with polypectomy, and colonoscopy was performed by experts in a controlled environment. In Intergroup 0089, however, colonoscopy and other surveillance procedures were performed in a wide variety of settings by a large number of practitioners.

We believe that this description of the diagnosis of second primary cancer in Intergroup 0089 reflects to some degree what is occurring in general practice. The quality of surveillance in Intergroup 0089 is more likely to be similar to community-based surveillance than to surveillance in the National Polyp Study. We also expect that surveillance in Intergroup 0089 occurred at least as often as it does in the community. Therefore, the rate of detected second primary colorectal cancer in the community can be expected to be at least as high as, if not higher than, in Intergroup 0089.

Second primary colon cancer found soon after original colon cancer may represent missed synchronous rather than metachronous cancer. Previous investigators have chosen cutoffs of 2 to 3 years to distinguish synchronous from metachronous cancer. Some of the early cases of second cancer in our study probably represent missed synchronous cancer. Because of this, we also compared incidence rates based only on second primary cancer that occurred after 2 years of follow-up. However, we believe that the choice of a fixed cutoff time is somewhat arbitrary and that as a practical issue, missed synchronous cancer is relevant precisely because it was missed. Our data suggest that both synchronous and metachronous cancer are sometimes missed, reflecting both the imperfect nature of surveillance and the failure to always examine the entire colon at the time of original diagnosis of colon cancer, either accurately or at all.

The distinction between synchronous and metachronous lesions becomes more important in decision making about surveillance. We therefore tried to ascertain the interval between surveillance and the detection of second primary colorectal cancer in patients most likely to have metachronous rather than missed synchronous cancer (patients who developed second cases of cancer after 2 years of follow-up). We found that in the 18 patients who developed second cancer after 2 years of follow-up, the median time from the most recent previous surveillance to diagnosis was 21 months. Of these patients, 78% had had a surveillance procedure within 3 years. In the 19 patients who had negative results on colonoscopy within 1 year of their original diagnosis but went on to develop second primary cancer, the median time to diagnosis of second primary cancer was 26 months. Thus, a significant percentage of patients developed second primary cancer less than 3 years after their most recent surveillance.

Our study has limitations. We lack family history data for most patients and therefore cannot completely exclude the possibility that second primary cancer occurred in patients with hereditary nonpolyposis colorectal cancer. However, we looked at two surrogates for hereditary nonpolyposis colorectal cancer, right-sided first primary colon cancer and young age (data not shown), and found that neither was a risk factor for second primary cancer. Nevertheless, with only 42 events, our power to detect a small increase in risk was limited. This question would be better examined in a cohort with more events that would also allow identification of other risk factors that define subsets of patients at highest risk for second cancer.

Collection of data on surveillance was not a predetermined aim of our study, and therefore the accuracy of this information is not known. It is possible that what was called a "colonoscopy" on follow-up forms could have been another surveillance procedure, such as flexible sigmoidoscopy. Furthermore, recent data suggesting that barium enema and flexible sigmoidoscopy may not be adequate screening tools for colon cancer may make these tests less common in the future (17). The most likely error, however, is underreporting of surveillance frequency, which would make our data even more convincing.

Our study does not address whether more frequent surveillance would have decreased the incidence of second primary colorectal cancer or led to earlier diagnosis. Our analysis of surveillance in Intergroup 0089 is purely descriptive. Moreover, any recommendations for a change in surveillance strategy must also consider the economic costs of surveillance and complications associated with colonoscopy. However, we believe our data show that in practice, despite surveillance, rates of second primary cancer will remain at least as high as rates of first primary cancer in the general population and significantly higher than would be expected from the National Polyp Study. What interventions, if any, should be performed to decrease the incidence of second primary colorectal cancer remain to be determined.

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Change in Lung Function and Morbidity from Chronic Obstructive Pulmonary Disease in α_1-Antitrypsin *MZ* Heterozygotes: A Longitudinal Study of the General Population

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Background: A deteriorating effect of severe α_1-antitrypsin deficiency (*ZZ* genotype) on lung function is well known, whereas the role of intermediate deficiency (*MZ* genotype) remains uncertain.

Objective: To test the hypothesis that *MZ* intermediate α_1-antitrypsin deficiency affects pulmonary function and disease.

Design: Population-based cohort study with 21-year follow-up.

Setting: Copenhagen, Denmark.

Participants: 9187 adults randomly selected from the Danish general population.

Measurements: Plasma α_1-antitrypsin levels, annual decrease in FEV_1, airway obstruction, and hospitalization and mortality from chronic obstructive pulmonary disease (COPD).

Results: 451 participants (4.9%) carried the *MZ* genotype. Plasma α_1-antitrypsin levels were 31% lower in *MZ* heterozygotes than in persons with the *MM* genotype (Student *t*-test, $P <$ 0.001). Annual decrease in FEV_1 was 25 mL in *MZ* heterozygotes and 21 mL in persons with the *MM* genotype (*t*-test, $P = 0.048$). Airway obstruction was found in 19% of *MZ* heterozygotes compared with 15% of *MM* carriers (chi-square test, $P = 0.023$); in a logistic regression analysis adjusted for age, sex, and tobacco consumption, the corresponding odds ratio was 1.3 (CI, 1.0 to 1.7). The incidence of hospitalization and mortality from COPD was 32 cases per 10 000 person-years in persons with the *MZ* genotype and 22 cases per 10 000 person-years in those with the *MM* genotype (log-rank test, $P = 0.063$). In a Cox regression model adjusted for age, sex, tobacco use, and FEV_1 at study entry, relative risk for COPD outcomes in persons with the *MZ* genotype versus persons with the *MM* genotype was 1.5 (CI, 1.0 to 2.3). All these results were independent of the *S* and *E* alleles in this gene and were not affected by cystic fibrosis Δ*F508* heterozygosity.

Conclusions: *MZ* heterozygotes had a slightly greater rate of decrease in FEV_1 and were modestly over-represented among persons with airway obstruction and COPD. In the population at large, *MZ* heterozygosity may account for a fraction of COPD cases—on the order of 2%, similar to the percentage of persons with COPD who have the severe but rare *ZZ* genotype.

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Chronic obstructive pulmonary disease (COPD) is one of the most important health problems worldwide (1, 2). More than 90% of COPD cases are caused by smoking, but only a fraction of smokers develop this disease. The variability in COPD expression among smokers could be due to differences in the environment, in genetic predisposition, or both.

So far, severe α_1-antitrypsin deficiency has been the best described genetic risk factor for COPD (2, 3). When lung tissue is α_1-antitrypsin deficient, protection from neutrophil elastase is impaired and elastic tissue is slowly destroyed, ultimately leading to reduced lung function and development of COPD (4). Severe α_1-antitrypsin deficiency is almost entirely caused by the presence of the *Z* alleles in the α_1-antitrypsin gene rather than the normal *M* allele. Relative plasma α_1-antitrypsin concentrations are approximately 16% for persons with the *ZZ* genotype, 83% for persons with the *MZ* genotype, and 100% for persons with the *MM* genotype (5). A deteriorating effect of severe α_1-antitrypsin deficiency (the *ZZ* genotype) on lung function has been known for many years (2–4), whereas the role of intermediate deficiency (the *MZ* genotype) remains uncertain (6, 7).

We previously performed a cross-sectional study of the at-large population in Denmark that assessed the *MZ* genotype and risk for lung disease. We found that *MZ* heterozygosity was associated with reduced pulmonary function in persons with clinically established COPD but not in persons without the disease (who account for 98% of the population) (8). However, *MZ* heterozygosity may lead to increased annual loss of lung function and increased COPD risk in the average person during prolonged follow-up. Furthermore, other genetic variability in the α_1-antitrypsin gene may influence the association between the *MZ* genotype and lung function

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and disease. Although we previously considered the other well-known structural mutation in α_1-antitrypsin, the *S* allele, we had not considered the effect of the known variation in the α_1-antitrypsin promotor, the *E* allele (9). Finally, genetic variation in the cystic fibrosis gene may also influence lung function and disease (10), and we had not considered this in our former work (8).

The *E* polymorphism is a known (9) but infrequently studied variation of the α_1-antitrypsin gene that is situated in the 3′ noncoding enhancer binding region. This polymorphism may temper the increase in plasma α_1-antitrypsin concentrations that normally occurs during an acute-phase response but does not affect the baseline levels (11). The more severe *Z* and *S* polymorphisms, which are located in the coding regions of the gene, cause the protein to self-polymerize in the liver before secretion into the blood, thereby reducing baseline α_1-antitrypsin concentrations (4, 12).

Using 21-year follow-up data and triple measurements of lung function (obtained in 1976 to 1978, 1981 to 1983, and 1991 to 1994), we now report on the relationship between *MZ* heterozygosity and pulmonary function and disease in greater detail. We compared 10 different genotype combinations of the *Z*, *S*, *E*, and *M* alleles with respect to α_1-antitrypsin levels in plasma, annual decrease in FEV_1, spirometry-defined airway obstruction, and hospitalization or death from COPD. We also examined whether the common *ΔF508* mutation in the cystic fibrosis gene influences these associations. For these purposes, we studied a sample of 9187 persons in the Danish general population from the Copenhagen City Heart Study.

METHODS

Participants and Study Protocol

We studied participants in the Copenhagen City Heart Study, a prospective epidemiologic study in Denmark initiated in 1976 to 1978 (13, 14). A sample of 19 698 persons at least 20 years of age was randomly selected after stratification of the Copenhagen residents into 5-year age groups. From 1976 to 1978, participants were invited to complete a survey and then undergo a physical examination at Copenhagen University Hospital. All participants were subsequently invited to participate in a second questionnaire and physical examination from 1981 through 1983 and a third survey and examination from 1991 through 1994. Additional persons in the youngest age group were invited to participate after 5 years ($n = 500$) and 15 years ($n = 3000$). A total of 14 223 participants (response rate, 74%) attended the first examination, 12 698 (response rate, 70%) attended the second examination, and 10 135 (response rate, 61%) attended the third examination. Of the 10 135 persons who participated in the third survey and examination, 9259 provided blood samples and 9187 underwent genotyping for the *M*, *Z*, *S*, and *E* alleles and the *ΔF508* mutation in the cystic fibrosis gene (10). Details of the procedures for sample selection and the examination and characteristics of the persons who did not respond to the study survey are described elsewhere (8, 13, 14). Less than 1% of the participants were not white, and 99% were of Danish descent. All participants gave informed consent before entering the study. The ethics committee for the cities of Copenhagen and Frederiksberg approved the study.

Context

The clinical importance of α_1-antitrypsin heterozygosity is uncertain.

Contribution

This Danish population-based study followed 9187 participants (451 of whom were heterozygotes) with questionnaires and rep eated pulmonary function testing for up to 18 years. Compared with persons who had the normal (*MM*) genotype, heterozygotes had a slightly greater rate of decrease in lung function, slightly higher incidence of chronic obstructive pulmonary disease (COPD), and slightly higher occurrence of hospitalization or death from COPD.

Implications

Because the incidence of α_1-antitrypsin heterozygosity in the general population is much higher than that of homozygosity, α_1-antitrypsin heterozygosity is a more important public health problem than homozygosity.

—The Editors

Study Questionnaire

Participants filled out a self-administered questionnaire. At the study examination, an investigator and the participant scrutinized this questionnaire to ensure that the responses were accurate. All participants reported whether they were current smokers, ex-smokers, or never-

Table 1. **Characteristics of Participants Sampled from the Danish General Population***

Variable	Participants, according to Genotype									
	MM	*ME*	*EE*	*ES*	*MS*	*SS*	*EZ*	*MZ*	*SZ*	*ZZ*
Women/men, *n/n*	3898/3139	604/495	26/20	23/18	245/214	9/3	11/15	253/198	7/3	3/3
Age at study entry, *y*	47 ± 0.2	46 ± 0.4	46 ± 1.9	49 ± 2.0	46 ± 0.6	48 ± 3.6	46 ± 2.5	48 ± 0.6†	48 ± 4.0	46 ± 5.1
FEV_1 at study entry, *% of predicted*	90 ± 0.2	90 ± 0.5	90 ± 2.6	90 ± 2.9	90 ± 0.8	95 ± 5.1	93 ± 3.5	91 ± 0.8	94 ± 5.6	75 ± 7.2†
Smoking before study entry, *pack-years*‡	15 ± 0.2	15 ± 0.5	15 ± 2.8	19 ± 2.9	16 ± 0.9	11 ± 5.9	11 ± 3.8	16 ± 0.9	16 ± 6.2	10 ± 7.2
Follow-up, *y*	19 ± 0.1	19 ± 0.2	19 ± 0.9	18 ± 1.0	19 ± 0.3	20 ± 1.9	18 ± 1.3	19 ± 0.3	19 ± 2.0	17 ± 2.6
Smoking during follow-up, *g/d*§	8.7 ± 0.1	8.6 ± 0.3	9.2 ± 1.5	9.9 ± 1.6	9.7 ± 0.5†	4.6 ± 2.9	8.8 ± 2.0	8.8 ± 0.5	9.9 ± 3.2	7.0 ± 4.1

* Data expressed with the plus/minus sign are the mean ± SE.
† $P < 0.05$ compared with *MM*. Age at study entry and smoking before study entry were examined by using the Mann–Whitney U test. FEV_1 at study entry was examined by using the Student *t*-test.
‡ Calculated as (daily tobacco use [g] × duration of smoking [y])/20 (in g/pack).
§ The average amount of tobacco used (in g/d) at the different examinations attended.

smokers. Lifetime tobacco exposure before study entry was estimated in pack-years by multiplying daily tobacco consumption (in g) by the smoking duration (in years) and then dividing this number by 20 (g/pack). Smoking during follow-up (in g/d) was determined at each examination by self-report of the average amount of tobacco consumed daily.

Spirometry

At the first and second examinations, FEV_1 and forced vital capacity (FVC) were measured by using an electronic spirometer (model N 403, Monaghan, Littleton, Colorado), which was calibrated daily with a 1-L syringe and was calibrated weekly against a water-sealed Godard spirometer. The instrument used at the third examination was a dry-wedge spirometer (Vitalograph, Maids Moreton, Buckinghamshire, United Kingdom) that was calibrated daily with a 1-L syringe. To ensure accurate measurements, three sets of measurements were obtained at each examination, and the values produced on at least two of the measurements obtained at an examination had to differ by less than 5%. We used the

Table 2. **Plasma α_1-Antitrypsin Levels according to α_1-Antitrypsin Genotype and Alleles and Stratified by Smoking Status**

Variable	All Participants (*n* = 592)			Nonsmokers (*n* = 303)		
	α_1-Antitrypsin Level*	Change from *MM/M* (95% CI)	*P* Value†	α_1-Antitrypsin Level*	Change from *MM/M* (95% CI)	*P* Value†
	mg/mL	%		*mg/mL*	%	
Genotype						
MM (*n* = 115)	1.59 ± 0.02			1.53 ± 0.03		
ME (*n* = 114)	1.58 ± 0.02	0 (−4 to 4)	>0.2	1.55 ± 0.03	1 (−4 to 6)	>0.2
EE (*n* = 46)	1.66 ± 0.04	5 (0 to 10)	0.071	1.59 ± 0.05	4 (−4 to 11)	>0.2
ES (*n* = 40)	1.46 ± 0.04	−8 (−14 to −2)	0.005	1.42 ± 0.06	−8 (−16 to 1)	0.075
MS (*n* = 114)	1.41 ± 0.02	−11 (−15 to −7)	<0.001	1.36 ± 0.03	−11 (−17 to −6)	<0.001
SS (*n* = 12)	1.20 ± 0.07	−24 (−34 to −15)	<0.001	1.10 ± 0.08	−28 (−39 to −17)	<0.001
EZ (*n* = 26)	1.06 ± 0.05	−33 (−40 to −27)	<0.001	1.04 ± 0.06	−32 (−41 to −23)	<0.001
MZ (*n* = 109)	1.10 ± 0.02	−31 (−35 to −26)	<0.001	1.03 ± 0.03	−32 (−38 to −27)	<0.001
SZ (*n* = 10)	0.72 ± 0.08	−54 (−65 to −44)	<0.001	0.51 ± 0.13	−67 (−84 to −49)	<0.001
ZZ (*n* = 6)	0.33 ± 0.10	−79 (−92 to −66)	<0.001	0.36 ± 0.12	−77 (−92 to −62)	<0.001
Average allele effect‡						
M	1.57			1.51		
E	1.57	0		1.53	1	
S	1.39	−11		1.33	−12	
Z	1.07	−32		1.00	−34	

* Data expressed with the plus/minus sign are the mean ± SE. Information on smoking was not available for 3 participants (2 *MZ*, 1 *ES*).
† *P* values are for the comparison with *MM* carriers in the same group and were calculated by using the Student *t*-test.
‡ Average allele effect (in the following example, for the *Z* genotype) was calculated as $f_{Z/Z}\,E_{Z/Z} + 1/2\,f_{S/Z}\,E_{S/Z} + 1/2\,f_{E/Z}\,E_{E/Z} + 1/2\,f_{M/Z}\,E_{M/Z}/f_Z$, where f_Z is the allele frequency of *Z* (determined by gene counting), $f_{Z/Z}$ is the expected Hardy–Weinberg frequency of individuals with the *Z/Z* genotype, and $E_{Z/Z}$ is the average plasma α_1-antitrypsin level for individuals with the *Z/Z* genotype (21).

highest set of FEV_1 and FVC at each of the three examinations in our analyses as absolute values and as percentage of predicted values by using internally derived reference values based on a subsample of healthy never smokers (15). We considered participants to have airway obstruction if they met each of the following criteria at least once during the study: 1) FEV_1 less than 80% of the predicted value and 2) FEV_1/FVC less than 0.7 (16). Most participants with airway obstruction had COPD; however, 22% of the participants with airway obstruction reported having asthma. Whether self-reports of asthma were based on a physician's diagnosis or the participant's misconception of COPD could not be evaluated. To calculate annual change in FEV_1 (in mL/y), the most recently obtained FEV_1 (in mL) was subtracted by the FEV_1 value obtained at the first measurement, this difference was multiplied by 365.25, and this product was divided by the number of days between the two FEV_1 measurements (in years^{-1}).

COPD

Study classification of COPD required COPD as the main diagnosis by a physician at discharge or on the death certificate. The information on COPD diagnoses, which were drawn from the Danish National Hospital Discharge Register (data from 1976 to 1997 were available) and the Danish Register of Causes of Death (data from 1992 to 1999 were available), were based on the World Health Organization International Classification of Diseases, 8th or 10th edition (diagnosis codes 490–2 and J40–4, respectively) (17, 18).

Table 2—**Continued**

	Smokers (n = 286)	
α_1-Antitrypsin Level*	**Change from *MM/M* (95% CI)**	***P* Value†**
mg/mL	%	
1.65 ± 0.04		
1.63 ± 0.04	−1 (−7 to 4)	>0.2
1.73 ± 0.05	5 (−3 to 12)	>0.2
1.49 ± 0.05	−10 (−17 to −2)	0.013
1.46 ± 0.03	−11 (−17 to −6)	<0.001
1.39 ± 0.13	−16 (−32 to 0)	0.044
1.07 ± 0.07	−35 (−44 to −26)	<0.001
1.18 ± 0.04	−28 (−34 to −22)	<0.001
0.81 ± 0.10	−51 (−63 to −39)	<0.001
0.28 ± 0.18	−83 (−105 to −61)	<0.001
1.63		
1.61	−1	
1.44	−11	
1.14	−30	

Genotype Analysis

We identified the *Z* (342Glu→Lys), *S* (264Glu→Val), and *E* (1237G→A) (9) polymorphisms in the α_1-antitrypsin gene by performing polymerase chain reaction (PCR). We used the 5′ ATAAGGCTGTGCTGACCATCGTC 3′ (sense) and 5′ TTGGGTGGGATTCACCACTTTTC 3′ (antisense) primers to identify the *Z* allele, the 5′ TGAGGGGAAACTACAGCACCTCG 3′ (sense) and 5′ AGGTGTGGGCAGCTTCTTGGTCA 3′ (antisense) primers to identify the *S* allele, and the 5′ GTTCCTGAATAGCCCCTGTGGTA 3′ (sense) and 5′ CGGTATCCATTGATTAGACTGAA 3′ (antisense) primers to identify the *E* allele. The presence of the three polymorphisms (*Z*, *S*, and *E*) destroyed a Taq1 site in the respective PCR products. Fragments of 157 base pair (bp) and 22 bp (normal allele) or 179 bp (*Z* allele), 100 bp and 21 bp (normal allele) or 121 bp (*S* allele), and 258 bp and 59 bp (normal allele) or 317 bp (*E* allele) were separated on a 3% agarose gel. The *ΔF508* deletion in the cystic fibrosis transmembrane conductance regulator gene was identified as previously described (10).

Plasma α_1-Antitrypsin

Plasma α_1-antitrypsin levels were measured in all participants with the *EE* (n = 46), *ES* (n = 40), *EZ* (n = 26), *SS* (n = 12), *SZ* (n = 10), or *ZZ* (n = 6) genotype and in randomly selected subgroups of the other genotypes examined (109 of the participants with the *MZ* genotype, 114 with *MS*, 114 with *ME*, and 115 with *MM*). Using a two-sided significance level of 0.05 and a power of 95%, with the aim not to overlook a mean difference in α_1-antitrypsin levels between *MZ* and *MM* genotypes that was 75% of the difference previously determined (5), we estimated that we needed at least 100 participants of each genotype for our analyses (19). We used commercially available antisera (rabbit antihuman alpha-1-antitrypsin, DAKO A/S, Glostrup,

Table 3. **Annual Decrease in FEV$_1$ by α_1-Antitrypsin Genotype and Alleles, Stratified by Smoking Status**

Variable	All Participants (n = 6428)			Nonsmokers (n = 2379)			Smokers (n = 4049)		
	Annual Decrease in FEV$_1$*	*P* Value†	Change from *MM/M* (95% CI)	Annual Decrease in FEV$_1$*	*P* Value†	Change from *MM/M* (95% CI)	Annual Decrease in FEV$_1$*	*P* Value†	Change from *MM/M* (95% CI)
	mL/y		%	*mL/y*		%	*mL/y*		%
Genotype									
MM (n = 4914)	21 ± 0.5			13 ± 0.7			25 ± 0.6		
ME (n = 751)	19 ± 1.3	>0.2	−7 (−20 to 5)	15 ± 1.9	>0.2	16 (−16 to 48)	22 ± 1.6	0.037	−15 (−28 to −1)
EE (n = 36)	22 ± 5.8	>0.2	6 (−49 to 61)	13 ± 10	>0.2	−2 (−162 to 159)	25 ± 6.9	>0.2	1 (−53 to 55)
ES (n = 28)	27 ± 6.6	>0.2	31 (−32 to 93)	23 ± 12	>0.2	73 (−118 to 264)	28 ± 7.7	>0.2	13 (−47 to 73)
MS (n = 334)	22 ± 1.9	>0.2	7 (−12 to 26)	17 ± 3.3	>0.2	30 (−21 to 81)	24 ± 2.3	>0.2	−4 (−22 to 15)
SS (n = 8)	26 ± 12	>0.2	24 (−92 to 141)	19 ± 13	>0.2	44 (−162 to 250)	46 ± 25	>0.2	83 (−110 to 277)
EZ (n = 16)	31 ± 8.7	>0.2	50 (−32 to 133)	29 ± 13	>0.2	124 (−82 to 330)	32 ± 11	>0.2	28 (−59 to 114)
MZ (n = 329)	25 ± 1.9	0.048	19 (0 to 38)	20 ± 2.9	0.021	55 (8 to 101)	27 ± 2.5	>0.2	8 (−12 to 28)
SZ (n = 7)	56 ± 13	0.008	169 (45 to 294)	2 ± 33	>0.2	−86 (−590 to 419)	65 ± 14	0.006	156 (45 to 268)
ZZ (n = 5)	32 ± 16	>0.2	57 (−90 to 204)	1 ± 23	>0.2	−95 (−452 to 262)	54 ± 20	0.162	113 (−45 to 271)
Average allele effect‡									
M	21			16			26		
E	20		−4	17		8	22		−12
S	23		13	20		22	25		−3
Z	26		26	21		28	31		19

* Data expressed with the plus/minus sign are the mean ± SE.

† *P* values are for the comparison with *MM* individuals in the same group by using the Student *t*-test.

‡ Average allele effect (in this example, for *Z*) was calculated as $f_{Z/Z} E_{Z/Z} + 1/2 f_{S/Z} E_{S/Z} + 1/2 f_{E/Z} E_{E/Z} + 1/2 f_{M/Z} E_{M/Z}/f_Z$, where f_Z is the allele frequency of *Z* (determined by gene counting), $f_{Z/Z}$ is the expected Hardy–Weinberg frequency of individuals with the *Z/Z* genotype, and $E_{Z/Z}$ is the average annual change in FEV$_1$ for individuals with the *Z/Z* genotype (21).

Denmark) and Behring Nephelometer Analyzer II (Dade Behring, Deerfield, Illinois). The coefficients of variance were 9% at the 2.6-mg/mL level (n = 19) and 4% at the 1.1-mg/mL level (n = 19).

Statistical Analysis

We performed all statistical analyses using SPSS software (20). Among the many genotypes and alleles examined, we focused our analyses on whether the *ME, EE, ES, MS, SS, EZ, MZ, SZ,* or *ZZ* genotype differed from the *MM* genotype. We calculated average allele effects as described elsewhere (21).

To compare genotypes, we used the Student *t*-test, Mann–Whitney U test, or Pearson chi-square test. We examined whether the *MZ* genotype together with Δ*F508* heterozygosity or with tertile of tobacco use predicted annual change in FEV$_1$ by using two-way interaction terms between *MZ* genotype and covariate in an analysis of covariance; significance was measured according to the F statistic.

In each logistic regression analysis, which was unadjusted or adjusted for sex, decile of age, and decile of tobacco use, we examined the role of the α_1-antitrypsin genotype in predicting airway obstruction by using odds ratios with 95% CIs.

We plotted the combined cumulative incidence of COPD hospitalization and death during follow-up by using Kaplan–Meier curves and used the log-rank test to measure statistical significance between genotypes. Using Cox regression analysis unadjusted or adjusted for sex, decile of age, decile of tobacco use, and decile of FEV$_1$ at study entry, we examined the role of genotype on time to first hospitalization or time to death from COPD by using hazard ratios (relative risks) with 95% CIs. We tested possible interactions between *MZ* genotype and Δ*F508* heterozygosity or tertile of tobacco use in predicting COPD outcomes by using two-factor interaction terms; the likelihood ratio test determined the level of significance.

Role of the Funding Sources

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RESULTS

Of the 9187 persons in our analysis who underwent genotyping, 592 had measurements for plasma α_1-antitrypsin level and 6428 had values for annual decrease in FEV_1 (spirometry was performed in these participants at two or three examinations); 9159 persons were examined for airway obstruction (spirometry was performed at least once). Follow-up for COPD hospitalization and death was complete for all 9187 participants.

Frequencies of α_1-Antitrypsin Genotype

The relative frequencies of the α_1-antitrypsin genotypes in this sample of the white Danish general population were 0.766 for the *MM* genotype, 0.120 for *ME*, 0.005 for *EE*, 0.004 for *ES*, 0.050 for *MS*, 0.001 for *SS*, 0.003 for *EZ*, 0.049 for *MZ*, 0.001 for *SZ*, and 0.001 for *ZZ*. These frequencies did not differ significantly from those predicted by the Hardy–Weinberg equilibrium (chi-square test: for *M*, *E*, and *Z*, $P > 0.2$; for *S*, $P = 0.117$) and did not differ between women and men (chi-square test, $P > 0.2$). Table 1 shows the basic characteristics of the Copenhagen City Heart Study participants in our analysis.

α_1-Antitrypsin Genotype and Plasma α_1-Antitrypsin Levels

Compared with persons who have the *MM* genotype, the average plasma α_1-antitrypsin level was 8% lower in persons with the *ES* genotype, 11% lower in persons with *MS*, 24% lower in persons with *SS*, 33% lower in persons with *EZ*, 31% lower in persons with *MZ*, 54% lower in persons with *SZ*, and 79% lower in persons with *ZZ* (Table 2). The plasma α_1-antitrypsin levels in persons with the *ME* or *EE* genotype were similar to those in persons with the *MM* genotype. All these results were similar in smokers and nonsmokers. Compared with the plasma α_1-antitrypsin level in persons who had the *M* allele, the plasma α_1-antitrypsin level was 11% lower in persons with the *S* allele and was 32% lower in persons with the *Z* allele; the average plasma α_1-antitrypsin level for the *E* allele was similar to that for the *M* allele.

α_1-Antitrypsin Genotype and Annual Decrease in FEV_1

Compared with a 21-mL average annual decrease in FEV_1 in persons with the *MM* genotype, the average

Table 4. **Airway Obstruction and Chronic Obstructive Pulmonary Disease according to α_1-Antitrypsin Genotype by using Logistic and Cox Regression***

Genotype	Airway Obstruction					Chronic Obstructive Pulmonary Disease				
	Total Participants	Participants with Airway Obstruction (95% CI)	*P* Value†	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	Participants	Incidence	*P* Value†	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
	n	%				*n*	*n/10 000 person-years*			
MM	7018	15 (14–16)		1.0	1.0	7037	22		1.0	1.0
ME	1095	15 (13–17)	>0.2	1.0 (0.8–1.2)	1.0 (0.9–1.2)	1099	23	>0.2	1.1 (0.8–1.4)	1.0 (0.8–1.4)
EE	46	11 (4–24)	>0.2	0.7 (0.3–1.7)	0.6 (0.2–1.7)	46	57	0.028	2.6 (1.1–6.3)	2.3 (0.9–5.6)
ES	40	30 (17–46)	0.009	2.4 (1.2–4.7)	2.1 (1.0–4.4)	41	41	>0.2	1.9 (0.6–5.8)	1.1 (0.3–3.4)
MS	456	16 (13–20)	>0.2	1.1 (0.8–1.4)	1.0 (0.8–1.3)	459	27	>0.2	1.2 (0.8–1.8)	1.1 (0.7–1.7)
SS	12	0 (0–26)	0.144	–	–	12	0	>0.2	–	–
EZ	26	11 (2–30)	>0.2	0.7 (0.2–2.4)	0.7 (0.2–2.5)	26	0	>0.2	–	–
MZ	450	19 (16–23)	0.023	1.3 (1.0–1.7)	1.3 (1.0–1.7)	451	32	0.063	1.4 (1.0–2.1)	1.5 (1.0–2.3)
SZ	10	40 (12–74)	0.028	3.7 (1.1–13)	3.1 (0.8–13)	10	103	0.014	4.8 (1.2–19)	4.3 (1.0–17)
ZZ	6	67 (22–96)	<0.001	11 (2.1–61)	22 (3.5–134)	6	192	<0.001	9.4 (2.3–38)	12 (3.0–52)

* Odds ratios and 95% CIs for other covariates included in multifactorial (adjusted) logistic regression analysis: age (20–28 y, 1.0; 29–35 y, 1.8 [1.1–3.0]; 36–39 y, 3.3 [2.1–5.3]; 40–42 y, 4.2 [2.6–6.7]; 43–46 y, 5.1 [3.2–7.9]; 47–49 y, 6.9 [4.4–11]; 50–53 y, 9.9 [6.4–15]; 54–56 y, 8.8 [5.6–14]; 57–62 y, 11 [6.9–16]; 63–89 y, 11 [6.8–16]), sex (men, 1.0; women, 0.7 [0.6–0.8]), and tobacco consumption (0 g/d, 1.0; 1–3 g/d, 1.1 [0.8–1.5]; 4–6 g/d, 1.8 [1.4–2.3]; 7–9 g/d, 2.3 [1.8–2.9]; 10–11 g/d, 1.9 [1.4–2.5]; 12–14 g/d, 3.3 [2.6–4.2]; 15–16 g/d, 2.6 [2.0–3.3]; 17–18 g/d, 3.5 [2.8–4.4]; 19–20 g/d, 3.2 [2.0–5.1]; 21–24 g/d, 3.1 [2.5–3.8]; 25–96 g/d, 2.8 [2.2–3.6]). Relative risks and 95% CIs for other covariates included in multifactorial (adjusted) Cox regression analysis: age (20–28 y, 1.0; 29–35 y, 2.3 [0.6–9.2]; 36–39 y, 2.4 [0.7–8.4]; 40–42 y, 4.6 [1.4–16]; 43–46 y, 6.1 [1.9–20]; 47–49 y, 9.2 [2.9–30]; 50–53 y, 10 [3.3–33]; 54–56 y, 10 [3.2–33]; 57–62 y, 11 [3.4–34]; 63–89 y, 11 [3.5–35]), sex (men, 1.0; women, 0.9 [0.7–1.1]), tobacco use (0 g/d, 1.0; 1–3 g/d, 1.6 [1.0–2.7]; 4–6 g/d, 1.8 [1.1–2.9]; 7–9 g/d, 1.8 [1.2–2.9]; 10–11 g/d, 3.1 [2.1–4.7]; 12–14 g/d, 2.5 [1.7–3.8]; 15–16 g/d, 3.3 [2.2–5.0]; 17–18 g/d, 2.8 [1.9–4.2]; 19–20 g/d, 2.2 [1.0–4.8]; 21–24 g/d, 2.6 [1.8–3.8]; 25–96 g/d, 3.1 [2.1–4.6]), and FEV_1 % of predicted at study entry (112%–182%, 1.0; 105%–111%, 0.8 (0.3–2.7); 99%–104%, 2.3 (0.9–5.9); 95%–98%, 2.2 (0.9–5.8); 91%–94%, 2.0 (0.8–5.3); 87%–90%, 3.5 (1.4–8.5); 83%–86%, 3.6 (1.5–8.7); 77%–82%, 5.4 (2.3–13); 69%–76%, 6.9 (3.0–16); 4%–68%, 20 [8.6–44]). Selected genotypes with outcomes of chronic obstructive pulmonary disease different from those for the *MM* genotype are shown as Kaplan–Meier curves in the Figure.

† The Pearson chi-square test or log-rank test compared participants with the *MM* genotype with persons with other genotypes.

annual decrease was 19% greater in persons with the *MZ* genotype and 169% greater in persons with the *SZ* genotype (**Table 3**). When participants were stratified by smoking status, the finding in *MZ* heterozygotes was significant in nonsmokers only, while the finding in *SZ* compound heterozygotes was significant in smokers only. Other genotypes did not differ significantly from the *MM* genotype. The *S* and *Z* alleles, respectively, had annual decreases in FEV_1 that were 13% and 23% greater than that of the *M* allele; the annual decrease associated with the *E* allele was similar to that for the *M* allele.

α_1-Antitrypsin Genotype and Airway Obstruction

Thirty percent of the persons with the *ES* genotype ($P = 0.009$), 19% of persons with the *MZ* genotype ($P = 0.023$), 40% of persons with the *SZ* genotype ($P = 0.028$), and 67% of persons with the *ZZ* genotype ($P < 0.001$) had airway obstruction compared with 15% of persons with the *MM* genotype (**Table 4**). The percentage of persons with airway obstruction was similar for other genotype groups compared with the *MM* group. After adjustment for age, sex, and tobacco use, the equivalent odds ratios for airway obstruction compared with the *MM* genotype were 2.1 (CI, 1.0 to 4.4) for the *ES* genotype, 1.3 (CI, 1.0 to 1.7) for *MZ*, 3.1 (CI, 0.8 to 13) for *SZ*, and 22 (CI, 3.5 to 134) for *ZZ*.

α_1-Antitrypsin Genotype and Hospitalization or Death from COPD

The incidence of COPD outcomes per 10 000 person-years was 22 cases in the *MM* group compared with 57 in the *EE* group ($P = 0.028$), 32 in the *MZ* group ($P = 0.063$), 103 in the *SZ* group ($P = 0.014$), and 192 in the *ZZ* group ($P < 0.001$) (**Figure** and **Table 4**). In a Cox regression model adjusted for age, sex, tobacco consumption, and percentage of FEV_1 predicted at study entry, the equivalent relative risks for COPD outcomes compared with persons who had the *MM* genotype were 2.3 (CI, 0.9 to 5.6) in persons with the *EE* genotype, 1.5 (CI, 1.0 to 2.3) in those with *MZ*, 4.3 (CI, 1.0 to 17) in those with *SZ*, and 12 (CI, 3.0 to 52) in those with *ZZ*.

Context-Dependent Associations for *MZ* Heterozygosity

MZ heterozygosity did not interact with $\Delta F508$ heterozygosity or smoking status in predicting annual change in FEV_1 ($P > 0.2$ for both comparisons) or in predicting COPD outcomes (for $\Delta F508$ heterozygosity, $P = 0.166$; for smoking status, $P > 0.2$).

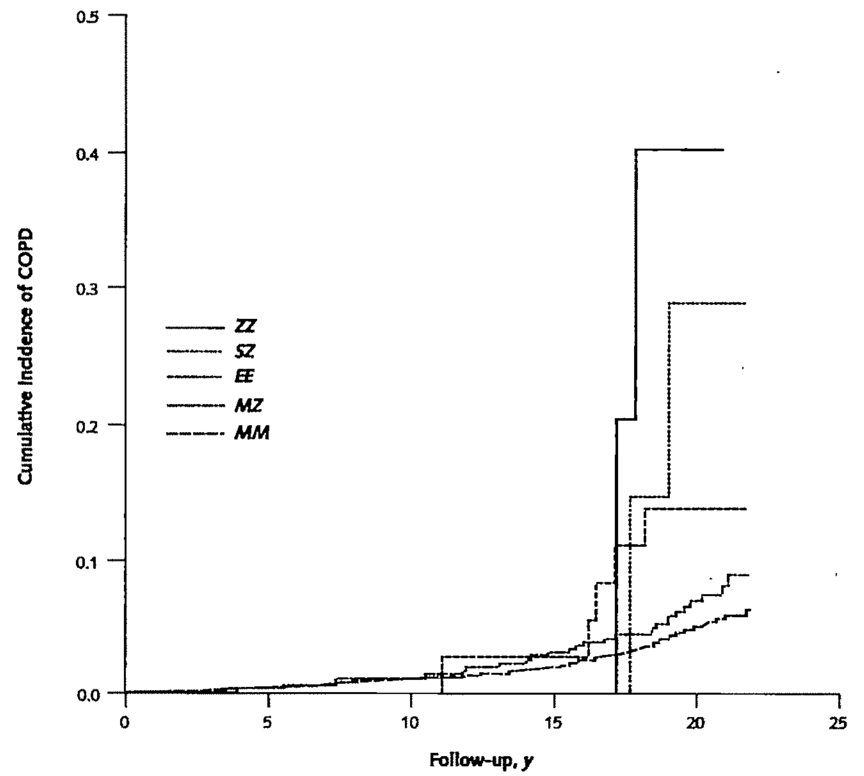
DISCUSSION

In this large longitudinal study of the Danish general population, *MZ* heterozygotes had decreased plasma α_1-antitrypsin levels, a slightly increased annual decrease in FEV_1, were modestly over-represented among persons with airway obstruction, and had a modestly higher incidence of COPD compared with persons who had the *MM* genotype. These findings were independent of the *S* and *E* alleles in the α_1-antitrypsin gene and were not affected by cystic fibrosis $\Delta F508$ heterozygosity.

Whether *MZ* heterozygosity is a risk factor for COPD has been controversial for many years (6, 7), perhaps because the association is relatively subtle and thus difficult to detect in sufficient numbers in traditional clinical series. However, because the frequency of the *MZ* genotype in the general population is high (1 in 20 persons in Denmark), even a small effect of the *MZ* genotype on decrease in lung function may contribute to the risk for COPD in the general population, as our study indicates.

In agreement with some (22, 23) but not all (24–26) previous longitudinal studies, *MZ* heterozygotes in our study had a 19% greater rate of decrease in lung function than did persons with the *MM* genotype. Similarly, *MZ* heterozygotes had a 30% increased risk for airway obstruction and a 50% increased risk for COPD. In the largest pervious report on this subject (27), in which *MZ* heterozygotes were identified mainly as family members of *ZZ* index cases, the relative risk for obstructive pulmonary disease in *MZ* heterozygotes compared with persons who had the *MM* genotype was 3.4 (CI, 2.2 to 5.3) in the first-degree relatives and 1.3 (CI, 0.7 to 2.2) in other relatives. The results from that study agree with our findings of a risk estimate of 1.3 (CI, 1.0 to 1.7) for airway obstruction and a risk estimate of 1.5 (CI, 1.0 to 2.3) for COPD in persons with the *MZ* genotype. Using the latter value, we can estimate as an attributable fraction (28) that the *MZ* genotype may account for approximately 2.4% of COPD cases in the current sample. In contrast, we found that *ZZ* homozygosity accounted for only approximately 0.8% of the COPD cases in our study, and this finding confirms

Figure. **Kaplan–Meier curves showing combined cumulative incidence of hospitalization and death due to chronic obstructive pulmonary disease (*COPD*) during follow-up.**



Persons at Risk, *n*					
MM	7037	6152	5584	5490	4413
MZ	451	408	377	369	293
EE	46	44	38	36	28
SZ	10	10	9	9	5
ZZ	6	5	5	5	2

Only selected genotypes with COPD outcomes different from the *MM* genotype are shown. The number of persons at risk at the beginning of each 5-year period is shown at the bottom of the figure.

results of a previous study (8). Therefore, *MZ* heterozygosity probably accounts for at least as many cases of COPD in the population at large as does the severe α_1-antitrypsin *ZZ* deficiency.

As did previous studies (4, 7), we found that persons with the *SZ* or *ZZ* genotype had a lower average plasma α_1-antitrypsin level and a nominally greater decrease in lung function compared with *MM* individuals. In our study, decrease in lung function was not significantly greater in persons with the *ZZ* genotype than in persons with the *MM* genotype, and this may be explained by the limited number of *ZZ* homozygotes and the fact that lung function was already lower at study entry in persons with the *ZZ* versus the *MM* genotype.

Compared with the risks for persons with the *MM* genotype, persons with the *EE* genotype had an increased risk for COPD, and persons with the *ES* genotype had an increased risk for airway obstruction. However, because the persons with the *EE* or *ES* genotypes had no increase in risk for airway obstruction and COPD (unlike the *MZ*, *SZ*, and *ZZ* genotypes), and neither genotype was associated with excess decrease in lung function, our observations may represent chance findings. Nevertheless, we cannot exclude the possibility that the *E* allele may be associated with COPD, as has been suggested in some (9, 29) but not all (30–32) previous studies on this subject.

To identify factors that could intensify the effect of

MZ heterozygosity on decrease in lung function, we tested for interactions between other pulmonary risk factors and *MZ* heterozygosity. We found that heterozygosity for the cystic fibrosis $\Delta F508$ mutation or the α_1-antitrypsin *E* mutation did not influence the association between *MZ* heterozygosity and decrease in lung function. In contrast with previous results (24), our findings indicate that smoking did not interact with genotype on decrease in lung function.

A potential limitation of our study is that participants underwent genotyping only if they attended the third examination (1991 to 1994). Thus, selection bias may have occurred if death or severe lung disease prevented some *MZ* heterozygotes from participating in the third survey; however, the observed genotype frequencies did not differ from those predicted by the Hardy–Weinberg equilibrium at any of the three examinations (in 1976 to 1978: for *M*, *E*, and *Z*, $P > 0.2$; for *S*, $P = 0.186$; in 1981 to 1983: for *M*, *E*, *S*, and *Z*, $P > 0.2$; in 1991 to 1994: for *M*, *E*, and *Z*, $P > 0.2$; for *S*, $P = 0.117$). Nevertheless, if such a bias exists, we may have underestimated the effect of the *MZ* genotype on decrease in lung function. Bias caused by investigator knowledge of disease or risk factor status seems unlikely because our sample was selected from the general population and because genotyping of our sample was performed without investigator knowledge of disease status or lung function test results. Misclassification of genotypes is unlikely because the identification of *MZ* included a control site for restriction enzyme digestion and because all participants with the *EE*, *ES*, *SS*, *EZ*, *SZ*, or *ZZ* genotype were reanalyzed to confirm the diagnosis. Finally, two investigators separately scrutinized all database entries.

In conclusion, *MZ* heterozygotes had, on average, plasma α_1-antitrypsin levels that were 31% lower and a rate of FEV_1 decrease that was 19% greater than the average values in persons with the *MM* genotype; the *MZ* heterozygotes had an odds ratio for airway obstruction of 1.3 (CI, 1.0 to 1.7) and a relative risk for COPD of 1.5 (CI, 1.0 to 2.3). In Denmark, the fraction of COPD cases that can be attributed to *MZ* heterozygosity is similar to that attributed to the severe but uncommon α_1-antitrypsin deficiency due to *ZZ* homozygosity. Nevertheless, the 50% increase in risk for COPD in *MZ* heterozygotes compared with persons who have the *MM* genotype is relatively small for the individual; thus, our data should not be used to suggest that the entire population should be tested for α_1-antitrypsin genotype. Testing for *MZ* heterozygosity in patients with COPD could help identify patients who are genetically susceptible to COPD. In the future, after more COPD susceptibility genes have been identified, screening for several such mutations may allow physicians to classify patients with COPD according to low, middle, or high genetic susceptibility; this could lead to different management of COPD. Today, however, diagnosing *MZ* heterozygosity in COPD patients will not alter management unless α_1-antitrypsin supplements are eventually found to improve long-term COPD outcomes in *MZ* heterozygotes. Because the *Z* allele accounts for 95% of α_1-antitrypsin deficiency in Europe and North America, our findings may apply to other parts of the world—in particular, to white populations—beyond Scandinavia.

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The Stool Antigen Test for Detection of *Helicobacter pylori* after Eradication Therapy

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Background: **Current noninvasive tests to confirm the eradication of *Helicobacter pylori* must be performed 4 weeks or more after eradication therapy is completed.**

Objective: **To determine whether the stool antigen test, a relatively new noninvasive test for *H. pylori*, administered at various times after eradication therapy correctly identifies persons with persistent *H. pylori* infection.**

Design: **Prospective blinded study.**

Setting: **Six clinical centers in the United States and Europe.**

Patients: **84 *H. pylori*–infected patients undergoing endoscopy for upper abdominal symptoms.**

Measurements: **At baseline and on day 35 after the completion of triple eradication therapy, all patients underwent endoscopy with histologic examination, rapid urease test and culture, urea breath test, and a stool antigen test. The stool antigen test was also performed on days 3, 7, 15, 21, 28, and 35 after completion of therapy.**

Results: **Compared with the gold-standard endoscopic tests on day 35 after antimicrobial therapy, the urea breath test had a sensitivity of 94% (95% CI, 71% to 100%) and a specificity of 100% (CI, 94% to 100%). The stool antigen test had a sensitivity of 94% (CI, 71% to 100%) and a specificity of 97% (CI, 89% to 100%). On day 7 after treatment, the stool antigen test was predictive of eradication (positive predictive value, 100% [CI, 69% to 100%]; negative predictive value, 91% [CI, 82% to 97%]).**

Conclusion: **A positive result on the stool antigen test 7 days after completion of therapy identifies patients in whom eradication of *H. pylori* was unsuccessful.**

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Noninvasive tests for *Helicobacter pylori* are important in primary care, both for initial diagnosis of *H. pylori* infection and for confirmation of eradication. Current guidelines recommend noninvasive testing and treatment of young dyspeptic patients without alarm symptoms (such as dysphagia or weight loss that suggest underlying malignant disease) in a primary care setting by using low-cost noninvasive tests (1, 2). Randomized, controlled trials have shown that a "test and eradicate" strategy toward *H. pylori* is effective in patients with dyspepsia seen in primary care settings who have not undergone investigations such as endoscopy or radiographic studies (3). Post-therapy testing is also growing in importance. Resistant strains of *H. pylori* are now widely prevalent in the United States and Europe, and eradication therapy with current regimens fails in 10% to 20% of patients (4, 5). Furthermore, some patients with ulcer disease remain symptomatic despite successful eradication of *H. pylori* and healing of the ulcer (6). In patients with persistent symptoms, testing for persistent *H. pylori* infection is important to direct further therapy. Routine testing to confirm eradication in patients with complicated ulcer disease, such as bleeding peptic ulcer, is necessary because the risk for rebleeding is greatly increased in patients with persistent infection (7).

The choice of tests in the post-therapy setting is limited. Serologic tests are unreliable in determining eradication (8). Endoscopic tests (rapid urease test, histologic examination, or culture) are reliable, but endoscopy is expensive and inconvenient. Until recently, the only noninvasive test that reliably demonstrated whether eradication was successful was the urea breath test (9). This test has high sensitivity and specificity in the post-therapy setting but cannot be used until 4 weeks after treatment. Moreover, the breath test is still not widely available in the United States.

The fecal antigen test is a relatively new noninvasive test for detection of *H. pylori* (10). This test detects the presence of infection by measuring the fecal excretion of *H. pylori* antigens. It has been approved by the U.S. Food and Drug Administration for detection of *H. pylori* before and after therapy.

We sought to determine whether a stool antigen test administered at various times after treatment correctly

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identifies persons in whom *H. pylori* infection persists despite eradication therapy.

Context

Standard treatment regimens do not eradicate infection in approximately 10% to 20% of people with ulcers or gastritis caused by *Helicobacter pylori*.

Symptoms do not reliably identify patients who have persistent infection despite treatment.

Although positive results on a urea breath test done 4 weeks after treatment reliably identify persistent infection, a noninvasive test that detects successful eradication earlier would be useful.

Contribution

This multicenter study shows that a positive finding on a stool antigen test done as early as 1 week after treatment identifies about 95% (range, 70% to 100%) of cases of persistent infection.

Generalization Cautions

Findings are from patients with dyspepsia who were referred for endoscopy; 20% of patients were still infected at 1 month despite eradication therapy.

–The Editors

METHODS

We prospectively studied 84 patients infected with *H. pylori* at six clinical centers (31 in Bologna, Italy; 29 in Amsterdam, the Netherlands; 9 in Rome, Italy; 8 in Lisbon, Portugal; 4 in Madrid, Spain; and 3 in Milwaukee, Wisconsin). The sample consisted of consecutive patients with dyspepsia (defined as pain or discomfort centered in the upper abdomen) who were referred by primary care physicians for upper endoscopy (11). Consenting patients were enrolled if they tested positive for *H. pylori* on endoscopic tests. Patients enrolled in this study have not been enrolled in other studies. Patients were excluded if they had taken proton-pump inhibitors, H_2-receptor antagonists, nonsteroidal anti-inflammatory agents, or antibiotics in the 4 weeks before the study. Failure to return for follow-up endoscopy was an a priori exclusion criterion. All patients gave written informed consent, and the study was approved by the human subjects review committee or equivalent at each participating institution.

At baseline, patients underwent endoscopy with biopsy sampling for histologic examination (two samples from the antrum and two from the corpus), culture (two samples from the antrum and two from the corpus), and a rapid urease test (one sample from the antrum). All patients were infected with *H. pylori* at baseline, as demonstrated by positive results on both rapid urease testing and histologic examination or a positive culture for *H. pylori*. Within 24 hours of the endoscopy, all patients underwent a ^{13}C or ^{14}C urea breath test. The breath test was chosen according to local availability and experience, but in all cases a validated breath test analysis system was used. Cut-off values were determined according to the recommendations of the various manufacturers of these tests.

Patients collected stool using a kit consisting of a plastic spoon that is used to scoop a small amount of stool from the toilet paper or toilet bowl into an airtight container. At all sites, the stool assay was performed by using the Premier Platinum HpSA test (Meridian Diagnostics, Inc., Cincinnati, Ohio). The assay is a microwell-based enzyme immunoassay that uses polyclonal anti–*H. pylori* capture antibody adsorbed to microwells. Diluted patient samples and a peroxidase-conjugated polyclonal antibody were added to the wells and incubated at room temperature for 1 hour. A wash was performed to remove unbound material. Substrate was added and incubated for 10 minutes at room temperature. Color develops in the presence of bound enzyme. Stop solution was added, and the results were inspected spectrophotometrically at 450 nm within 15 minutes of adding the stop solution. Visual determination can also be used; this has been shown to have similar results (12). A positive control and a negative control are built into the test. The cut-off values were classified as negative (<0.140), indeterminate (0.140 to 0.159), or positive (>0.160).

After completion of the baseline procedures, treatment was begun with ranitidine bismuth citrate (400 mg twice daily) or omeprazole (20 mg twice daily) in combination with amoxicillin (1 g twice daily) and clarithromycin (500 mg twice daily) for 7 to 10 days. Seven-day eradication therapy was used in Europe, where it is approved by the European Union and has been shown to be effective (5). Ten-day triple therapy with proton-pump inhibitors was used in the United States, where it is approved by the U.S. Food

Table. **Use of Stool Antigen Test To Predict *Helicobacter pylori* Status 35 Days after Completion of Eradication Therapy**

Day after Start of Treatment	Stool Antigen Test Result*	*H. pylori*–Positive Patients (n = 17), n†	*H. pylori*–Negative Patients (n = 64), n‡	Probability That Patient Will Still Have *H. pylori* at Day 35 (95% CI)	Probability That Patient Will Be Free of *H. pylori* at Day 35 (95% CI)
3	Positive	3	1	0.75 (0.19–0.99)	–
	Negative	12	63	–	0.84 (0.74–0.91)
	Equivocal	2	0	–	–
7	Positive	10	0	1.0 (0.69–1.0)	–
	Negative	6	64	–	0.91 (0.82–0.97)
	Equivocal	1	0	–	–
15	Positive	14	1	0.93 (0.68–1.0)	–
	Negative	3	63	–	0.95 (0.87–0.99)
	Equivocal	0	0	–	–
21	Positive	14	0	1.0 (0.77–1.0)	–
	Negative	2	65	–	0.97 (0.89–1.0)
	Equivocal	1	1	–	–
28	Positive	14	0	1.0 (0.77–0.96)	–
	Negative	2	62	–	0.97 (0.89–1.0)
	Equivocal	1	2	–	–
35	Positive	16	1	0.94 (0.71–1.0)	–
	Negative	0	63	–	1.0 (0.94–1.0)
	Equivocal	1	0	–	–

* Positive results were $\geq$0.160 units on stool antigen test; negative results were $<$0.140 units on stool antigen test; equivocal results were 0.140 to 0.159 units on stool antigen test.

† Positive for *H. pylori* by biopsy or culture 35 days after start of treatment.

‡ Negative for *H. pylori* by biopsy or culture 35 days after start of treatment.

and Drug Administration. Patients collected stool for the stool antigen test on days 3, 7, 15, 21, 28, and 35 after completion of *H. pylori* eradication therapy. On day 35 after completion of eradication therapy, endoscopy was repeated and biopsy samples were again obtained for histologic examination, culture, and the rapid urease test, as performed at the baseline visit. The ^{13}C or ^{14}C urea breath test was repeated on day 35 by using the same method and cut-off values as at baseline. Patients were classified as being infected with *H. pylori* at baseline and having persistent infection on day 35 if culture of gastric biopsy specimens was positive for *H. pylori* or results of the rapid urease test and histologic examination were positive. All other patients were classified as negative. These criteria have been recommended by an expert panel for use in clinical trials of *H. pylori* eradication (13). At baseline, the sensitivity of the stool test and urea breath test were calculated by using the presence of infection (defined above) as the gold standard. At each time point after completion of therapy (days 3, 7, 15, 21, 28), predictive values were calculated by using continued infection on day 35 as the gold standard (positive result on culture or on rapid urease test and histologic examination).

Trained investigators who were blinded to the results of the other diagnostic studies performed the stool assays. The first endoscopy procedure was performed before the stool and breath tests. Therapy was given on the basis of results on endoscopic testing. Endoscopists were blinded to the results of post-treatment stool studies and the breath test until all evaluations were completed.

Long-Term Follow-up

Patients in whom eradication of *H. pylori* was successful were eligible for entry into a long-term study evaluating the stool antigen test. For 6 months, stool antigen tests were done monthly and a urea breath test was obtained every 3 months.

Statistical Analysis

Statistical analysis was performed by using StatView for Windows, version 5.01 (SAS Institute, Inc., Cary, North Carolina). Results are presented as the mean (±SD). Sensitivity, specificity, probabilities, and predictive values are presented with 95% exact binomial CIs. Equivocal stool tests are considered by inclusion in the denominator of sensitivity and specificity. Stool antigen concentrations at individual time points were compared by using the Mann–Whitney test with downward adjustment of the *P* values for repeated observations (14).

Role of the Funding Source

The manufacturer (Meridian Diagnostics, Inc) provided the stool kits. The study had no other funding source. Collection, analysis, and interpretation of the data, including the decision to publish, were solely the decision of the authors; the manufacturer of the test had no role in this process.

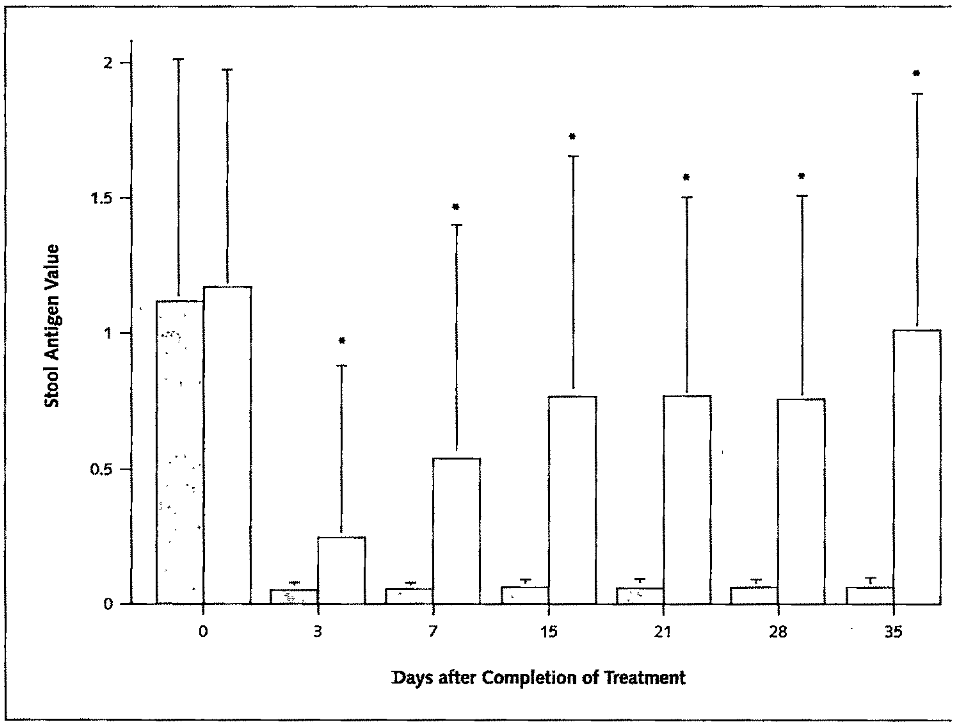
RESULTS

The mean age of the 84 study patients was 52 years (range, 18 to 81 years). Fifty-three patients were women, and 31 were men. Endoscopic findings were as follows: normal (7 patients), esophagitis (2 patients), erythema in the antrum (45 patients), erosions in the antrum (11 patients), erosive duodenitis (9 patients), duodenal ulcers (8 patients), gastric ulcer (2 patients). Despite repeated reminders, 3 patients did not return for follow-up endoscopy and were excluded from the analysis. Satisfactory breath and biopsy samples were obtained from all patients. Results of the stool test are shown in the **Table**.

At baseline (before treatment), only sensitivity could be calculated because the sample consisted only of *H. pylori*–infected patients. The sensitivity of the urea breath test at baseline was 99% (95% CI, 96% to 100%) (true-positive in 80 patients and false-negative in 1 patient). The sensitivity of the stool antigen test at baseline was 99% (CI, 96% to 100%) (true-positive in 77 patients, false-negative in 1 patient, and indeterminate in 3 patients).

Eighty-one patients were prescribed 7-day therapy, and 3 patients were prescribed 10-day therapy. Of the

Figure. **Mean stool antigen values over time in patients with (*gray bars*) and without (*white bars*) eradication of *Helicobacter pylori*.**



Extensions of the bars represent the SD. The stool antigen value was determined spectrophotometrically. The time point of 0 represents baseline (before eradication therapy). Subsequent time points are measured from completion of eradication therapy. $^*P < 0.05$ compared with patients in whom *H. pylori* was eradicated.

81 patients who completed the study, 78 received 7-day therapy and 3 received 10-day therapy. The overall eradication rate was 79% (66 patients). Compared with the gold-standard endoscopic tests on day 35, the urea breath test had a sensitivity of 94% (CI, 71% to 100%; true-negative in 64 patients, true-positive in 16 patients, and false-negative in 1 patient) and a specificity of 100% (CI, 94% to 100%). The stool antigen test had a sensitivity of 94% (CI, 71% to 100%; true-negative in 63 patients, true-positive in 16 patients, false-positive in 1 patient, and indeterminate in 1 patient) and a specificity of 97% (CI, 89% to 100%). The result on rapid urease test was positive in all patients with positive findings on histologic examination.

The mean stool antigen concentration at baseline did not significantly differ (1.11 ± 0.89) between patients who eventually had successful eradication and patients without successful eradication (1.16 ± 0.81). In patients with successful eradication, the stool antigen values decreased into the negative range for the stool assay (below the cut-off value of 0.140) 3 days after completion of therapy and remained in this range for the remainder of the study. Three days after antimicrobial treatment was stopped, stool antigen concentrations were significantly higher in patients with persistent infection (**Figure**) and continued to be significantly higher at days 7, 15, 21, 28, and 35. The **Table** shows the value of a positive or negative test result in predicting eradication (determined by the gold standard test on day 35).

Nineteen of 66 patients with successful eradication of *H. pylori* in the initial phase of the study agreed to participate in a long-term study and were followed for 6 months. Stool specimens were collected monthly, and the urea breath test was administered at 3 and 6 months. Results of the urea breath test and the stool antigen test remained negative in every patient at each time point throughout this follow-up.

DISCUSSION

Several diagnostic tests are available for *H. pylori*. They may broadly be divided into tests that indirectly determine the presence of the microorganism (antibody tests in blood, urine, or saliva) or direct tests that detect the intact organism (histology and culture), antigens shed from the organism (stool antigen test), or metabolic functions of the organism (rapid urease test and urea breath test). Although indirect tests are the mainstay of initial diagnosis in primary care, they are not reliable after therapy (15). The performance of a test after therapy depends on that test's characteristics. Several studies have shown that the rapid urease test, the breath test, and histologic examination may be falsely negative during the first few weeks after therapy (9). Current guidelines therefore recommend use of the urea breath test 4 weeks after completion of therapy (16).

The stool antigen test has been widely studied in the initial (pretreatment) diagnosis of *H. pylori* infection. The largest study reported to date included 501 patients undergoing endoscopy and a ^{13}C urea breath test (10). Patients were considered positive if they had a positive result on rapid urease testing and histologic examination or a positive culture for *H. pylori*. The stool test had a high sensitivity and specificity compared with the urea breath test. Studies from the United States have had similar results (17).

In the post-therapy setting, a multicenter European trial evaluated the sensitivity and specificity of the stool test and the urea breath test (compared with multiple endoscopic tests as the gold standard) 4 weeks after eradication therapy in 235 patients (18). The gold standard for comparisons in that study was histologic examination plus culture. The sensitivity of the stool test was 95.6% (CI, 89.6% to 100%), and the specificity was 94.7 (CI, 91.5% to 97.9%), values similar to those in our study. A smaller (142 patients) single-center study reported poorer results, with a sensitivity of 70% (CI, 50% to 86%) and a specificity of 82% (CI, 75% to 89%) 6 weeks after completion of eradication therapy (19). In that study, a single test (urea breath test) was used as the gold standard for eradication.

The choice of gold-standard test greatly affects the results of noninvasive testing for *H. pylori* (20). Use of a single test as the gold standard increases the error rate. The European *Helicobacter pylori* Study Group proposed that in comparative studies, the gold standard should consist of at least two tests that differ from the ones being examined (13). Similarly, the U.S. Food and Drug Administration limits the use of single tests in the evaluation of *H. pylori* infection status (21). This agency considers a positive culture to be evidence of *H. pylori* infection before and after treatment. A positive result on histologic examination after eradication is considered evidence of persistent *H. pylori* infection, but a negative result on histologic examination alone is not adequate to confirm eradication. We used three independent tests (rapid urease test, histology, and culture) as the gold standard to provide the most accurate assessment of *H. pylori* status. Our gold standard would meet the criteria of the U.S. Food and Drug Administration and the European *Helicobacter pylori* Study Group.

We found that in patients in whom eradication is successful, stool antigen concentrations decrease rapidly after completion of eradication therapy. In patients in whom eradication has failed, stool antigen concentrations increase rapidly after completion of such therapy. It is currently recommended that the urea breath test to determine whether *H. pylori* eradication be done at least 4 weeks after completion of therapy because the test is not reliable at earlier time points. This is sometimes a problem in clinical practice because some patients remain symptomatic after antimicrobial therapy or develop recurrent symptoms shortly after treatment is completed. In these patients, a stool antigen test performed 7 days after completion of therapy may help direct further therapy, and a second course of antimicrobial therapy can be administered without further delay if the stool test result is positive. Other patients in whom retesting should be considered are those who develop recurrent symptoms, those with a bleeding ulcer at initial presentation who are likely to have recurrent bleeding if they remain infected with *H. pylori*, and those who request confirmation of eradication. The predictive values of the stool test depend on the prevalence of the infection in the study sample. With modern therapy, eradication rates are high, both in controlled trials and in community practice; the prevalence of *H. pylori* infection after therapy should therefore be similar to that in our study (22). Eradication rates in our study are consistent with those in recent multicenter studies and may be related to increased rates of antimicrobial resistance in the population (23).

The choice of test after therapy depends on its cost and availability. In Europe, the urea breath test is inexpensive and widely available, but in the United States, this test is considerably more expensive and is still not generally available. Currently, Medicare reimburses the urea breath test at $103.95 (codes 83103 and 4). The stool antigen test does not have a specific code at this time but is reimbursed at $50 in most states (under code 87338) (24).

Our study has limitations. Patients were referred for endoscopy and may not be representative of patients with dyspepsia seen in primary care settings. However, the endoscopic findings in our study were similar to those reported in unselected patients undergoing endoscopy in primary care settings (25, 26). In addition, the sample size was modest, resulting in relatively wide CIs.

We conclude that a positive result on stool antigen testing 7 days after completion of therapy identifies patients in whom eradication of *H. pylori* was unsuccessful.

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COMMENTARY

This study is interesting because it illustrates the contrast between two ways in which physicians use tests. Sometimes, we use a test to predict a future event. More often, we use a test to predict the concurrent true state of the patient. Vaira and colleagues emphasize the former of these uses. They show us that performing positive stool antigen tests as recently as 1 week after antibiotic therapy helps predict persistent *Helicobacter pylori* infection 35 days later (probability, 69% to 100%). The authors correctly presented this result as a probability rather than as a measure of test performance, such as

Table. **Likelihood Ratio, Sensitivity, and Specificity of the Stool Antigen Test**

Stool Antigen Value at Day 35	Positive for *Helicobacter pylori* (*n* = 17), *n*	Negative for *Helicobacter pylori* (*n* = 64), *n*	Probability of Test Result If Disease Is Present	Probability of Test Result If Disease Is Absent	Likelihood Ratio (95% CI)*	Sensitivity	Specificity
≥0.160	16	1	0.94	0.016	60.2	–	–
0.140–0.159	1	0	–†	–†	–†	–	–
<0.140	0	63	0	0.98	0	–	–
≥0.160 as positive result	16	1	–	–	60.2 (29–74)	0.94	0.016
<160 as negative result	1	63	–	–	0.061 (0–0.23)	0.06	0.984

* The likelihood ratio is the probability of a test result if disease is present divided by the probability of the test result if disease is absent. According to Bayes theorem, the post-test odds of disease equals the pretest odds of disease times the likelihood ratio. Thus, the likelihood ratio is the amount by which a test result changes the odds of disease.
† Data for this range of test results were too sparse to calculate a meaningful measure of test performance.

sensitivity and specificity. They could calculate the latter only at day 35, when the reference standard test and the stool antigen test were performed together.

This study also illustrates the importance of reporting the test performance of all results, if possible. When a test such as the stool antigen test generates numbers on a continuous scale, the authors should ideally provide test performance data for defined values along the scale. In reality, most studies of test performance are too small to reliably estimate performance characteristics for many values. This study is a case in point. The authors classified the range of stool antigen results as positive (>0.160), equivocal (0.140 to 0.159), or negative (<0.140) (see the **Table** accompanying this commentary). According to the likelihood ratios, a stool antigen level greater than 0.160 increases the odds that *H. pylori* is present by a factor of 60, and a value less than 0.140 reduces the odds of *H. pylori* infection to zero. There were too few patients with equivocal stool antigen values to reliably estimate how much this result changes the odds that *H. pylori* is present. The authors could have defined a single cut-point (either 0.140 or 0.160) and combined the intermediate values with one of the other two groups. Many other studies (for example, studies of ventilation–perfusion lung scanning) have included enough patients with intermediate test results to make a valid estimate of the likelihood ratio and, thus, the information content of intermediate test results.

To report sensitivity and specificity when a test has many possible results, researchers must choose one value (the cut-point) that defines positive and negative results with respect to the study end point—in this case, failure to eradicate *H. pylori.* According to probability theory, the cut-point depends on the prevalence of disease and on the ratio of benefit gained by treating patients to the harm incurred. If the prevalence of disease is high or the benefits of treatment are high relative to the harms, one should choose a cut-point at which the test has a low likelihood ratio (that is, close to zero), so that a negative result implies a very low probability that disease is present. Either of the two possible cut-points (≥160 or ≥140) satisfy this criterion (**Table**).

What does the likelihood ratio tell us? It is the link between test performance and clinical practice. It tells us how much the odds change after a test result. Suppose the pretest odds of antibiotic therapy failure were 1 to 3 and the stool antigen test result was positive. The post-test odds would be the product of the pretest odds (1:3) and the likelihood ratio (60.2), or about 20:1—very strong evidence that the patient was still infected with *H. pylori.* If the test result had been negative, the post-test odds would be the product of 1:3 and 0.06, that is, 0.06:3, or 1:50, which is strong evidence that *H. pylori* infection is absent. These probability estimates imply that the stool antigen test should be useful in deciding whether to re-treat the patient. However, the wide CI of the likelihood ratio (0 to 0.23) when the test result is negative (<0.160) tells us to be cautious in interpreting a negative result.

—*The Editors*

Surprisingly Small Effect of Antiviral Treatment in Patients with Hepatitis C

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and Arthur J. McCullough, MD

Background: **The effect and applicability of interferon-based antiviral therapies in the general population of persons with hepatitis C virus (HCV) infection are unknown.**

Objective: **To determine the applicability and usefulness of antiviral therapy in a metropolitan clinic population.**

Design: **Retrospective case series of consecutively referred patients.**

Setting: **A teaching county hospital in Cleveland, Ohio.**

Patients: **327 patients referred to a liver clinic after a positive result for antibody against HCV on enzyme-linked immunosorbent assay (ELISA).**

Measurements: **Treatment rates; reasons for nontreatment.**

Results: **34 patients had no detectable HCV RNA. Of the remaining 293 patients, 72% were not treated for the following reasons: 37% did not adhere to evaluation procedures, 34% had medical or psychiatric contraindications, 13% had ongoing substance or alcohol abuse, 11% preferred no treatment, and 5% had normal liver enzyme levels. Only 83 patients (28%) were treated; 13% had a sustained viral response.**

Conclusion: **Most patients with HCV infection are not candidates for interferon-based therapies; alternative interventions should be sought for these patients.**

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Hepatitis C virus (HCV) infection is a major health problem. In the United States, approximately 4 million persons are infected with HCV, and 8000 to 10 000 persons die of HCV-related liver disease annually (1). The U.S. Centers for Disease Control and Prevention estimate that deaths from HCV infection will increase substantially and surpass those from HIV infection in 8 to 10 years (2). Currently, the recommended therapeutic strategy is to eradicate HCV infection by using interferon-based therapies, thereby potentially reducing HCV-related morbidity and mortality from the development of cirrhosis (3).

The average rate of sustained viral response with the combination therapy of interferon-α plus ribavirin (4, 5) and with pegylated interferon (6) range from 30% to 40%. However, these results may not represent the experience of the entire HCV-infected population because most studies have used highly selected patient groups, have been performed in referral centers, and have not reported screening sample size.

A trial in the United States (4), for example, excluded 404 of the 1337 screened patients, mostly because of selection criteria similar to those in the current study. Moreover, a large international trial (5) did not report screening data. Reports of treatment trials often do not clarify whether all patients or only potentially suitable study candidates were screened. Data are limited for important patient subgroups that do not fit the standard profile—for example, patients with active alcohol or substance abuse, children, homeless and incarcerated patients, elderly patients, and patients with comorbid conditions such as psychiatric disorders or autoimmune disease (7–10). Finally, cultural and educational characteristics may impede patient acceptance of treatment (11). Therefore, the extent to which the results of clinical trials in HCV-infected patients apply to the entire HCV-infected population is unknown. Several factors also may prevent use of antiviral treatment regimens. Side effects of interferon-based therapy are significant (10) and are similar with both standard and pegylated interferons (6).

We hypothesized that a substantial proportion of HCV-infected patients may not be candidates for currently available antiviral treatment. Therefore, we investigated the overall antiviral treatment rate and the reasons for nontreatment in a general population of HCV-infected patients in a metropolitan liver clinic.

METHODS

We reviewed the charts of new consecutive patients referred to the liver clinic at MetroHealth Medical Center in Cleveland, Ohio, because they had tested positive for HCV antibody on enzyme-linked immunosorbent assay (ELISA) during a 23-month period from January 1998 to November 1999. All patients were evaluated by one of two hepatologists who decided on treatment or nontreatment on the basis of previously agreed upon criteria. A specially trained nurse gave all patients a standardized comprehensive education program during their first office visit. Follow-up office appointments were scheduled for all appointments, and reminders were mailed for any missed office visits.

The criteria for treatment were a positive test result for HCV RNA and elevated levels of alanine aminotransferase or aspartate aminotransferase on two occasions during the preceding 6 months. The exclusion criteria were decompensated cirrhosis, other types of liver disease, active alcohol or drug use, nonadherence (missing >2 visits before treatment during the education process), poorly controlled psychiatric or seizure disorders, autoimmune disease, symptomatic cardiac disease, neutrophil count less than 1.5×10^9 cells/L and platelet count less than 0.75×10^9 cells/L, retinopathy, or cancer.

Context

Hepatitis C virus is the most common cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in the United States.

Trials show that about 50% of patients with chronic hepatitis C virus infection respond to prolonged treatment with antiviral drugs, such as pegylated interferon and ribavirin.

Physicians are selective about whom to treat because antiviral therapy is expensive and difficult to take and has many side effects.

Contribution

This study shows that 72% of patients with hepatitis C virus infection who attended an urban county clinic did not receive antiviral therapy because of failure to show up for appointments or tests, severe comorbid medical or psychiatric illness, ongoing alcohol or drug abuse, or preferences against treatment.

Implications

Most patients with chronic hepatitis C virus infection may not be good candidates for antiviral therapy.

–The Editors

RESULTS

Of the 327 patients who were evaluated after testing positive for HCV antibody, 34 patients (10%) had no detectable HCV RNA and therefore were not considered for treatment. Of the remaining 293 HCV-infected patients, 72% were not treated for the following reasons (**Figure**):

1. Nonadherence to evaluation and education—37%: These patients did not follow recommendations for evaluation; for example, they did not have blood drawn or attend the appointment for liver biopsy, or they missed more than two office appointments. Other complicating factors included homelessness or incarceration (the county prison system has had no established treatment protocol for persons with HCV infection).

2. Medical contraindication—34%: The most frequent contraindications were psychiatric disease, including poorly controlled severe depression, bipolar disease, and previous suicide attempt or specific ideation; decompensated cirrhosis; pregnancy; refusal to practice contraception; autoimmune disease; poorly controlled diabetes mellitus; or cytopenias.

3. Substance abuse—13%: Ongoing drug or alcohol use prevented these patients from receiving antiviral treatment.

4. Patient preference—11%: These patients chose not to be treated after considering possible side effects, treatment duration, family planning issues, or difficulties with injecting interferon after recovery from intravenous drug use. One patient declined treatment because of fear of high laboratory bills, despite free medications.

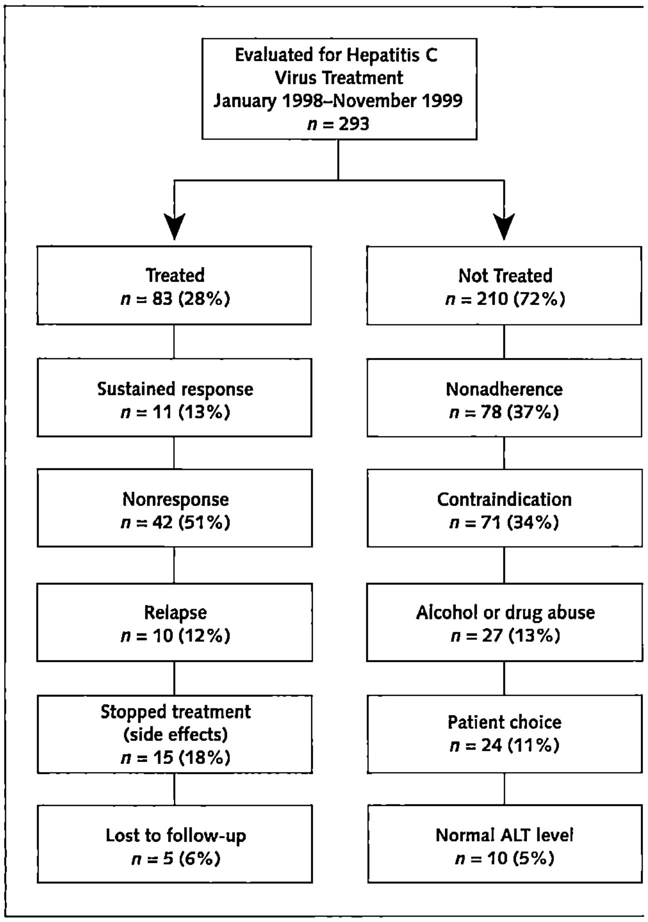
5. Normal alanine aminotransferase levels—5%: These patients were not treated, as per established treatment guidelines of the U.S. National Institutes of Health (12).

As shown in the **Figure**, only 83 of the 293 patients (28%) received interferon-based antiviral therapy, which consisted of interferon alone or interferon combined with ribavirin. Eleven patients (13%) had a sustained viral response, defined as an undetectable HCV RNA level 6 months after completing treatment. Thus, in the entire group of 293 patients who had tested positive for HCV RNA, the rate of sustained viral response was only 4%. Even if the sustained viral response rate were 40% (which is the mean rate reported for the more recent treatment regimens), only 11% of our total sample would have reached this end point.

In 52 (63%) of the 83 treated patients, viral eradication was not successful because of nonresponse (42 patients) or relapse (10 patients). Fifteen patients (18%) stopped treatment because of side effects, and 5 patients (6%) were lost to follow-up.

The treated and untreated groups did not differ significantly for age, sex, ethnicity/race, or risk factors. Although 72% of our patients were uninsured or were insured through Medicaid, financial status prevented treatment in only 1 patient. Liver biopsy was performed in 88% of treated patients and in 17% of untreated patients. Mild or moderate inflammation (Ishak stage 1 or 2) occurred more frequently in the untreated group (92% vs. 78%; $P < 0.05$); however, the proportion of patients with mild versus moderate fibrosis (Ishak stage 1 or 2) did not differ significantly (78% vs. 72%, respectively).

Figure. **Reasons for nontreatment with interferon in patients with hepatitis C virus infection.**



ALT = alanine aminotransferase.

Table. **Comparative Demographic Information on Patient Groups***

Variable	Study Group	NHANES Study†	MetroHealth Medical Center‡
All participants, *n*	327	386	909 805
Sex, %			
Male	63	65	36
Female	37	35	64
Mean age, y§	50	–	–
Ethnicity/race, %			
White	54	61	51
African American	35	20	35
Mexican or Hispanic	10	7	10
Other	1	12	4
Risk factors, %‖			
Injection drug use	66	–	–
Noninjection drug use	4	42	–
Blood transfusion	12	–	–
Other	7	–	–
None	22	–	–
Insurance status, %			
Medicaid	41	–	33
Medicare	6	–	14
Private insurance	22	–	32
No insurance	31	–	21

* NHANES = National Health and Nutrition Examination Survey.

† The NHANES study (1) only obtained data on marijuana and cocaine use as drug use–related risk factors for hepatitis C virus infection. Because data on other drug use, specifically intravenous drug use, were not obtained, total drug use in this sample is probably underestimated.

‡ The entire patient population at the MetroHealth Medical Center during the study period.

§ Ninety percent of patients in the current study were between 30 and 59 years of age. The NHANES study reported no data on this subject that would yield a meaningful comparison with the present study group.

‖ The percentage of all MetroHealth Medical Center patients with risk factors for hepatitis C virus infection is unknown.

The **Table** shows the characteristics of our HCV study group, the patients with HCV infection in the National Health and Nutrition Examination Survey (NHANES) (1), and the overall patient population at our medical center during the study period. There was no significant difference in sex between the two HCV groups, but the proportion of men in each of these groups was higher than in the overall population at our medical center. The NHANES group had a lower proportion of African-American patients and a higher proportion of patients classified in the "other" category for ethnicity/race. The NHANES study only obtained data on marijuana and cocaine use as risk factors. Because history of intravenous drug use was not obtained, total drug use in the NHANES population is probably underestimated compared with our study group. Compared with the entire MetroHealth Center population, our study group of patients with HCV infection had more uninsured persons and Medicaid recipients and had a smaller proportion of persons with private insurance or Medicare coverage.

DISCUSSION

As compared with previously reported treatment results from clinical trials (4–6), interferon-based therapies for HCV infection may be less useful in diverse HCV-infected populations. Most of the patients with HCV seen at our liver clinic, whose characteristics were similar to those of the HCV-infected patients in the general population described in NHANES (1), did not receive interferon-based treatment for the reasons shown in the **Figure**.

Preliminary data from a study in a clinic setting agree with our results (13). These researchers found that 41% of HCV-infected patients were untreated, primarily because patients declined to undergo therapy or had medical contraindications. Another preliminary study (14) found that receiving antiviral therapy depended on the type of medical facility at which the patient was seen: Only 34% of HCV-infected patients seen by community-based gastroenterologists received antiviral therapy compared with 64% at a tertiary referral center and 81% at a military medical center. The reasons for nontreatment in that study were similar to those in our study.

Because injection drug use and low socioeconomic status are currently the factors most strongly associated with HCV infection (15), our HCV-infected population—in whom the prevalence of intravenous drug use was 66% and the prevalence of low socioeconomic status was 72%—had risk factors that represent those of the general HCV-infected population. In fact, our data may overestimate the proportion of HCV-infected patients who receive treatment, because our study included few incarcerated persons; yet, approximately 31% to 50% of the 5 million incarcerated persons in the United States have HCV infection, and these cases of HCV infection go largely untreated (16).

In summary, these combined data indicate that a large proportion—perhaps the majority—of U.S. patients with chronic HCV infection are not candidates for interferon-based therapy. This information emphasizes the need to develop better-tolerated and more effective antiviral drugs (17), socioeconomically and culturally targeted screening programs (2, 11, 13), interventional strategies for substance abuse (18), and educational interventions to improve adherence to treatment and to decrease comorbid conditions, which increase the risk for progressive liver injury (19, 20).

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2001–2002 Series: Update Sessions from ACP–ASIM's 2001 Annual Session
Margaret Ring Gillock, Editor/David A. Cramer, MD, Co-Editor/Paul T. Kefalides, MD, Co-Editor

Update in Psychiatry

Robert K. Schneider, MD, and James L. Levenson, MD

Annals published its first Update in Psychiatry on 5 October 1999 (1) and the first Update in Addiction Medicine on 6 March 2001 (2). This Update is the first Update in Psychiatry presented at an Annual Session of the American College of Physicians–American Society of Internal Medicine. We see these Updates as steps toward creating a knowledge base of current evidence in psychiatry for internists that is on par with the knowledge bases of other medical specialties. This Update is broadly divided into the following categories: mood disorders, anxiety disorders, geropsychiatry, and new therapeutics.

Mood Disorders

Mood (affective) disorders often present in relapsing, remitting, and chronic forms or in combination with each other (for example, dysthymia and major depression are called "double depression"). Depressive disorders can also present with somatic symptoms as well as psychological symptoms. The reports summarized in this section address treatment of chronic depression, the risk for a recurrence of major depression, and physical symptoms and depression.

Treatment of Chronic Depression with a Combination of Medication and Psychotherapy Is Superior to Either Treatment Alone

Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med. 2000;342:1462-70. [PMID: 10816183]

Chronic depression is a significant source of impairment. At least 3% of the U.S. population has a chronic form of depression. Treatments for chronic depression have been varied, and few controlled clinical trials have examined treatment effects of psychotherapy or medications.

In a multicenter clinical trial, Keller and colleagues randomly assigned adults 18 to 75 years of age to receive nefazodone alone (not to exceed 600 mg/d), cognitive–behavioral psychotherapy alone, or a combination of the two therapies. The authors defined chronic depressive disorder as the presence of severe depressive symptoms for at least 2 years. The score on the Hamilton Rating Scale for Depression (HRSD) was the primary outcome measured.

The overall response rate (both remission and satisfactory response) was 48% in the nefazodone group and the psychotherapy group compared with 73% in the combined treatment group ($P < 0.001$). Nefazodone produced effects more rapidly than did psychotherapy: Significant advantages were evident in the first 4 weeks of nefazodone therapy. However, psychotherapy had a greater effect during the second part of the trial, and by week 12 the efficacy of the two approaches was similar. The combined treatment appeared to have an additive effect that became evident between weeks 4 and 5 and was sustained to the end of the 12-week trial. Adverse events occurred in 14% of the nefazodone group, 7% of the combined treatment group, and 1% of the psychotherapy group. The patients who withdrew from psychotherapy did so because they felt treatment was too time-consuming, they preferred medication, or they did not want psychotherapy.

Chronic depression is a debilitating illness commonly seen in primary care. This study highlights the value of the combination of psychopharmacology and cognitive–behavioral psychotherapy. It also suggests that for patients with chronic depression, physicians should address underlying abnormal depressed cognition and behaviors, which may be the result of years of depression, rather than simply targeting the symptoms with medications alone. A limitation of this study is the short duration of treatment (12 weeks) for a chronic disorder. Clinical experience suggests that chronic depression may take longer to respond to treatment.

Risk for Recurrence Increases with Each Episode of Depression, and Recurrence Is Less Likely as Time without Recurrence Increases

Solomon DA, Keller MB, Leon AC, et al. Multiple recurrences of major depressive disorder. Am J Psychiatry. 2000;157:229-33. [PMID: 10671391]

Major depression is an episodic disease, with recurrences affecting at least 50% of patients seeking treatment in

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tertiary referral centers (3). However, most studies have evaluated only one recurrence.

Solomon and colleagues studied multiple recurrences of unipolar major depression and assessed the risk for recurrence after recovery as part of the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression, a prospective, naturalistic, longitudinal, multicenter investigation of the episodic course of major depressive disorder. The study sample consisted of 366 patients with unipolar depression. Of the 318 patients who recovered from their intake episode of depression, 202 had a recurrence. Of these 202 patients, 172 recovered; 115 of these 172 patients had a second recurrence. The cumulative probability of recurrence for a patient with one recurrence at 1 year after recovery was 25%; at 2 years, 42%; and at 5 years, 60%. The cumulative probability of recurrence for a patient with two recurrences at 1 year after recovery was 41%; at 2 years, 59%; and at 5 years, 74%. The risk for recurrence progressively decreased as the duration of recovery increased. Of the original 366 patients, 48 did not recover from the index episode, 30 of 202 did not recover from the first recurrence, and 23 of 115 did not recover from the second recurrence. Although treatment was not controlled, it was documented. During the 4 weeks before the first three recurrences, 47% to 50% of all patients were receiving no treatment. During the 4 weeks before the fourth and fifth recurrences, one third of patients were still receiving no treatment.

Depression is the most common psychiatric illness. When considering discontinuation of treatment after recovery from a depressive episode, the clinician should know the risk for recurrence, incorporate this into the decision, and educate the patient about the risk. Solomon and colleagues' study underscores the frequently chronic nature of depression and the undertreatment of patients with recurrent depression. This study adds to the literature supporting the prolonged treatment of depression, particularly in its recurrent form.

Somatic Symptoms of Depression Are Common across Cultures, but There Are Important Differences in How Depressed Patients Present in Different Countries

Simon GE, VonKorff M, Piccinelli M, et al. An international study of the relation between somatic symptoms and depression. N Engl J Med. 1999;341:1329-35. [PMID: 10536124]

Patients with depression, especially those seen by nonpsychiatric physicians, frequently present with physical symptoms. Researchers have suggested that depressed patients in some countries or cultures are more likely to report somatic symptoms and are less willing to express emotional distress.

The World Health Organization's study of psychological problems in general health care screened 25 916 patients at 15 primary care centers in 14 countries on 5 continents. Of these, 5447 patients underwent a structured assessment of somatization and depression. The authors defined depression using criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, and used three definitions of somatization.

A total of 1146 of the 5447 patients (10.1%) met criteria for major depression. Of the patients with depression, 85% met at least one somatization definition, but there was little overlap among the definitions (only 4% of patients met all three). Across sites, the presence of psychological and physical symptoms varied widely but the balance of psychological to somatic symptoms was similar. When directly questioned, almost 90% of depressed patients admitted having psychological symptoms. This suggests that patients reporting somatic symptoms are neither unwilling nor unable to acknowledge psychological distress; rather, they may believe that reporting somatic symptoms is more appropriate when seeking help from a primary care physician. It is not surprising, then, that patients were more likely to express emotional distress to a physician with whom they already had a relationship.

Physical symptoms are a core component of major depression. This study adds to previous studies showing that depression can be readily diagnosed in primary care patients, even those who "somatize," by direct questioning about psychological symptoms. Physicians should always consider the possibility of depression in patients with disproportionate or unexplained physical symptoms and should not be too quick to diagnose a somatoform disorder (for example, somatization disorder or hypochondriasis). Physicians should be aware that patients from different countries or cultures will vary considerably in their readiness to volunteer information about both physical and psychological symptoms of depression.

ANXIETY DISORDERS

Anxiety disorders are almost as frequent as depressive disorders in primary care settings. Recent advances in psychopharmacologic and psychotherapeutic treatment have been made for generalized anxiety disorder, panic disorder, social phobia, and post-traumatic stress disorder.

Imipramine and Buspirone Facilitate Discontinuation of Long-Term Benzodiazepine Therapy

Rickels K, DeMartinis N, García-España F, et al. Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. Am J Psychiatry. 2000;157:1973-9. [PMID: 11097963]

Patients who have been taking long-term benzodiazepine therapy for chronic anxiety present a dilemma. Are they primarily dependent on benzodiazepines, or does their anxiety require long-term treatment? Answering this question requires gradually tapering the benzodiazepine dose, but patients are often reluctant to do so. Rickels and colleagues studied whether another drug (imipramine or buspirone) can facilitate discontinuation of benzodiazepine therapy.

The participants had generalized anxiety disorder and had been receiving long-term benzodiazepine treatment (mean, 8.5 years) despite an average of three unsuccessful previous attempts to stop using the drug. After stabilization, patients entered a randomized, controlled trial in which they received imipramine, buspirone, or placebo for 1 month before gradual tapering of benzodiazepines (4 to 6 weeks) and for 3 weeks after tapering.

The rate of success (being benzodiazepine-free 3 months later) was significantly higher for patients receiving imipramine (82.6%; $P < 0.01$) and for those receiving buspirone (67.9%; $P < 0.06$) than for placebo recipients (37.5%). Neither drug significantly reduced symptoms of benzodiazepine withdrawal.

This study suggests that even long-term benzodiazepine users who have been unsuccessful in previous tapering attempts can be withdrawn from benzodiazepines if they receive short-term imipramine treatment.

Venlafaxine Is Effective in Patients with Generalized Anxiety Disorders

Gelenberg AJ, Lydiard RB, Rudolph RL, et al. Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. JAMA. 2000;283:3082-8. [PMID: 10865302]

Generalized anxiety disorder is a common chronic condition that is often but not always associated with depression. Symptoms include excessive, uncontrollable pervasive anxiety with both psychological and physical manifestations (such as muscle tension and insomnia).

In a 6-month randomized, placebo-controlled trial, Gelenberg and colleagues tested the efficacy of venlafaxine in 251 outpatients with generalized anxiety disorder and without depression. The extended-release form of venlafaxine was used in doses adjusted to control symptoms (75 to 225 mg). Response rates during weeks 6 to 28 were 69% or higher in the venlafaxine group and 42% to 46% in the placebo group ($P < 0.001$). The most common side effects were nausea, somnolence, dry mouth, and male sexual dysfunction. The frequency of adverse effects decreased after the first 2 months.

The major limitation in this study was a high dropout rate (59%) during the double-blind phase. The most common reason for dropout was unsatisfactory response in the placebo group and adverse reactions in the venlafaxine group.

Limitations notwithstanding, this study suggests that extended-release venlafaxine is an effective, well-tolerated alternative to benzodiazepines for patients with generalized anxiety disorder.

Combination of Cognitive–Behavioral Therapy and Imipramine Improves Outcomes of Panic Disorder in Maintenance Phase

Barlow DH, Gorman JM, Shear MK, et al. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial. JAMA. 2000;283:2529-36. [PMID: 10815116]

Both drugs and psychological treatments have been shown to be effective individually for treating panic disorder. This study compared imipramine and cognitive behavioral therapy with placebo and with each other. It also compared combined treatment with each treatment alone. Patients were seen weekly for 3 months (acute phase); responders were then seen monthly for 6 months (maintenance phase) and then followed up for 6 months after treatment discontinuation.

Both imipramine and cognitive–behavioral therapy were significantly superior to placebo at the end of 3 months and even more so after 6 months of maintenance treatment. Among responders, imipramine produced a better response than did the other therapies. The response rate at the end of 3 months was higher for the combined treatment group than for the other groups, but this difference was not statistically significant. After 6 months of maintenance treatment, the response rate for combined therapy was superior to that with cognitive–behavioral therapy or imipramine alone.

Dropout during the 3-month short-term treatment was significant. Most patients who had responded at the end of 3 months (82% to 90%) completed maintenance treatment; in the placebo group, however, the rate was only 33%. Because patients were excluded if they had moderate to severe agoraphobia, the results may not be generalizable to patients with more severe panic disorder involving agoraphobia.

For many years, imipramine was considered the standard drug treatment for panic disorder. Most experts would now consider selective serotonin reuptake inhibitors (SSRIs) to be the first-line choice because these drugs purportedly have fewer side effects. This study should remind physicians that effective psychological therapies are available for panic (and other anxiety disorders) and that combining treatments can be advantageous. Ironically, during a period in which controlled clinical trials have shown the effectiveness of psychological therapies for anxiety disorders, fewer patients are receiving this form of therapy (4).

Paroxetine Is Efficacious for Social Phobia

Baldwin D, Bobes J, Stein DJ, et al. Paroxetine in social phobia/social anxiety disorder. Randomised, double-blind, placebo-controlled study. Paroxetine Study Group. Br J Psychiatry. 1999;175:120-6. [PMID: 10627793]

Social phobia (also known as social anxiety disorder) is a common, potentially disabling, and underdiagnosed condition characterized by intense fear of situations in which the person fears embarrassment or humiliation when interacting with other people. Specific psychological therapies, monoamine oxidase inhibitors, benzodiazepines, and SSRIs have shown some efficacy for treating this disorder. However, large controlled trials are needed to clearly delineate the role of treatment.

Baldwin and colleagues conducted a 12-week randomized, placebo-controlled trial to assess the efficacy of short-term paroxetine treatment of social phobia in 290 patients. Considerably more patients responded to paroxetine than to placebo (65.7% vs. 32.4%; $P < 0.001$) at the end of the study. Paroxetine was generally well tolerated. The results indicate that paroxetine is an effective treatment for patients with social phobia.

The investigators excluded patients who had had any other axis I psychiatric disorder in the 6 months preceding the study. Because social phobia frequently coexists with other anxiety and mood disorders, this exclusion limits the generalizability of the findings.

Many studies have shown a 5% to 8% prevalence of social phobia, yet the disorder is seldom diagnosed, let alone treated, in primary care settings. Other SSRIs, such as fluvoxamine, are also effective (5). Because some symptoms of social anxiety (for example, anxiety about public speaking) are extremely common in the general population, some question whether social phobia is really an illness. However, in essentially every study, patients with the full disorder of social phobia have a broad range of functional disabilities in occupational, educational, and other social roles (6). Physicians should also remember that psychotherapy for social phobia is effective but underused (4).

Sertraline Is an Effective Treatment for Post-Traumatic Stress Disorder

Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. JAMA. 2000;283:1837-44. [PMID: 10770145]

Post-traumatic stress disorder (PTSD) is a common and serious disorder that follows life-threatening traumatic experiences. Symptoms include persistent reexperiencing of the trauma (through flashbacks, nightmares, and intrusive memories), avoidance of reminders of the trauma, selective amnesia, emotional numbing, and increased arousal (for example, startled responses, hypervigilance, and insomnia). Few randomized, controlled trials have studied the efficacy of pharmacotherapy for PTSD.

To determine the efficacy of the SSRI sertraline in short-term treatment of PTSD, Brady and colleagues randomly assigned 187 outpatients with chronic PTSD (mean duration of illness, 12 years) to receive sertraline or placebo. The rate of response to sertraline at the end of 12 weeks was significantly better than the response to placebo (53% vs. 32%; $P < 0.008$). Insomnia was the only adverse effect reported significantly more often with sertraline than with placebo. These data support sertraline as an effective and well-tolerated short-term treatment of chronic PTSD.

Although most primary care physicians are experienced in prescribing SSRIs for depression, they may underdiagnose and undertreat PTSD. Improved recognition could lead to treatment and improved outcome. However, in general, drug therapy has been less effective than psychological therapies for treating PTSD (7). Post-traumatic stress disorder is a complex and often disabling illness, and primary care physicians should collaborate with mental health professionals in choosing treatments for a particular patient.

Geropsychiatry

Depression, cerebrovascular disease, and dementia are common in elderly patients. These conditions overlap both in clinical presentation and in causality, with important implications for diagnosis and treatment. Delirium is also a frequent challenge in older medically ill patients, and new practice guidelines were recently published. New research has also shed light on the drug treatment of agitation and psychosis in dementia. The newer antipsychotic drugs have some adverse effects of particular relevance to the treatment of medically ill and older patients.

Multiple White-Matter Lesions Are Associated with Late-Onset Depression

de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and depressive symptoms in elderly adults. Arch Gen Psychiatry. 2000;57:1071-6. [PMID: 11074873]

Cerebral white-matter lesions representing vascular disease have been implicated as an important etiologic factor in late-onset depression. de Groot and colleagues sought to determine the relationship between cerebral white-matter lesions and depression in the general population. They used magnetic resonance imaging to evaluate the presence and severity (maximal diameter) of subcortical and periventricular white-matter lesions in a community-based sample of elderly Dutch residents without dementia; they then screened for the presence (using the Center for Epidemiologic Studies–Depression scale) or history of depression.

Patients with severe white-matter lesions were three to five times more likely to have depressive symptoms than those with only mild or no white-matter lesions. Persons with severe subcortical but not periventricular white-matter lesions were more likely to have a history of depression with onset after age 60 years compared with persons who had only mild or no white-matter lesions. The relationship between white-matter lesions and depressed symptoms may be due to other factors, such as cognitive decline, ventricular enlargement, stroke, or cortical atrophy. However, the investigators found that the relationship between white-matter lesions and depressive symptoms did not change when they controlled for these possible confounding factors. Another possible explanation for the association could have been that depression increases the risk for vascular disease (rather than the other way around). If this were the case, however, one would have expected a stronger association with early-onset rather than late-onset depression.

This study adds to our growing awareness that vascular diseases, including coronary artery disease, stroke, and other cerebral vascular disease, increase the risk for development of depression. Physicians should be especially attentive in screening for depression among elderly patients who have evidence of vascular disease.

Depressive Symptoms Are Often Early Manifestations of Dementia

Chen P, Ganguli M, Mulsant BH, et al. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. Arch Gen Psychiatry. 1999;56:261-6. [PMID: 10078504]

Investigators have long recognized that depression and dementia frequently coexist in elderly patients, but the nature of the relationship remains controversial. Cognitive decline may precede depression, or depressive symptoms may develop before dementia. Should we regard whichever appears first as a risk factor or an early manifestation of the other illness?

As part of the Monongahela Valley Independent Elders survey, Chen and colleagues prospectively evaluated the temporal relationship between the appearance of depressive symptoms and the clinical onset of dementia in a community-based sample. The cohort consisted of 1366 patients 65 years of age or older who were assessed every 2 years; 97% of patients were white. The data in this study represent 8 years of serial, biannual evaluations.

Patients with dementia, especially Alzheimer disease, had an increased risk for developing depression compared with patients without dementia. Adjusted odds ratios for the development of depression were 6.5 (95% CI, 2.2 to 19.1) in patients with Alzheimer disease and 5.2 (CI, 1.8 to 15.2) in patients without dementia. Depressive symptoms did not increase the risk for developing dementia; depressive symptoms appear to be early manifestations rather than predictors of dementia. The co-occurrence of depression and dementia was seen only in a small subgroup of patients. This study does not refute the possibility that major depression may be a risk factor for dementia.

Apathy, social withdrawal, and poor concentration in the elderly commonly lead to referral for treatment of depression but may instead herald evolving dementia. Elderly patients with new onset of depressive symptoms should be screened by using a brief cognitive mental status examination at presentation and should be screened during follow-up for the development of dementia.

American Psychiatric Association Released Delirium Practice Guideline

Practice guideline for the treatment of patients with delirium. American Psychiatric Association. Am J Psychiatry. 1999;156(Suppl):1-20. [PMID: 10327941]

The prevalence of delirium in hospitalized medically ill patients is 10% to 30%, with higher rates in subgroups (for example, patients in the postoperative period, terminally ill patients). Essential features of delirium include disturbance of consciousness, attention, cognition, and perception.

The American Psychiatric Association has published a useful practice guideline for the treatment of patients with delirium. The guideline was developed by a panel of experts who conducted a systematic, comprehensive literature review (1966 through 1998) and reached final consensus conclusions after extensive review by external organizations and other experts. A summary of the major conclusions follows.

Delirium in medically ill patients is associated with longer hospital stays, increased medical morbidity, and increased mortality. Although not always possible, the first priority in intervention is identifying a cause. Many validated instruments are now available to diagnose delirium and rate severity of delirium symptoms. Electroencephalography usually shows generalized slowing but is not helpful in distinguishing specific causes of delirium. Environmental interventions are generally recommended for all patients with delirium. These include providing an optimal level of stimulation, reducing sensory impairments, making environments more familiar, and providing environmental cues to facilitate orientation. Cognitive supportive measures, such as providing patients with reorientation, reassurance, and information about delirium, are helpful. In addition, providing similar information and support to family members can be beneficial. Antipsychotic medications are usually the pharmacologic treatment of choice. Because patients receiving antipsychotic drugs for delirium have occasionally developed prolonged QT intervals, sometimes leading to torsades de pointes, electrocardiographic assessment is indicated. The major limitation in the development of this practice guideline was the paucity of systematic data. Delirium is difficult to study, but this guideline represents the state of the art for management of delirium.

Olanzapine and Risperidone Reduce Aggression and Psychosis in Patients with Dementia

Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry. 2000; 57:968-76. [PMID: 11015815]

Katz IR, Jeste DV, Mintzer JE, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. J Clin Psychiatry. 1999;60:107-15. [PMID: 10084637]

Patients with dementia frequently manifest psychotic and disruptive behavioral symptoms, including delusions, hallucinations, aggression, and agitation. Street and Katz and their colleagues tested the efficacy and safety of the newer antipsychotic drugs olanzapine and risperidone in treating such psychotic and behavioral disturbances. Both studies were multicenter, double-blind, placebo-controlled trials in institutionalized elderly patients with dementia. Each study assessed more than one drug dose.

Both drugs significantly reduced aggression and psychosis at relatively low doses. Extrapyramidal symptoms were significantly more common at 2 mg of risperidone per day than at 1 mg per day. One mg per day was recommended as the most appropriate dosage. Somnolence and gait disturbance were the most common adverse effects of olanzapine; a dosage of 5 to 10 mg per day was recommended as optimal.

Low doses of the newer antipsychotic drugs appear effective and well tolerated in treating psychotic behavioral disturbances in elderly patients with dementia. Haloperidol has previously been shown to be safe and effective for this purpose. Although haloperidol is considered less expensive than the newer agents, its long-term use poses a much higher risk for tardive dyskinesia. The newest antipsychotics have been associated with a much lower incidence of persistent tardive dyskinesia in elderly patients with dementia (8). Both studies had a 25% to 30% dropout rate, and both were conducted for relatively short periods (6 weeks for olanzapine, 12 weeks for risperidone). As a result, they do not answer questions about long-term efficacy and safety.

Internists caring for patients with dementia, particularly those in nursing homes, should be aware that these medications can reduce patients' distress and caregivers' burden and may even reduce the need for nursing home placement.

Newer Antipsychotic Drugs Have Some Medical Complications

Although psychiatrists usually handle prescriptions of antipsychotic drugs, internists must be aware of their potential medical complications. Clozapine causes agranulocytosis in approximately 1% of patients, but this has not been a concern with the other new antipsychotics. A common problem with both the traditional and newer antipsychotics has been weight gain. The greatest weight gain has been experienced with clozapine and olanzapine (9). The only antipsychotic drug available in the United States that has not been associated with weight gain is molindone (10) and perhaps ziprasidone, the newest antipsychotic. Although the newer antipsychotics are free or relatively free of extrapyramidal syndromes compared with the older drugs, all of the newer drugs have caused neuroleptic malignant syndrome (11). Many case reports have described new-onset diabetes or ketoacidosis in patients already known to have diabetes who received each of the new antipsychotics. A recent prospective study of 82 patients receiving clozapine found that diabetes was diagnosed in almost 40% during 5-year follow-up. Although weight gain was common, it was not a significant risk factor for the development of diabetes (12). These authors also found an increase in serum lipid levels. In a short-term prospective study of 14 patients receiving olanzapine (median duration, 5 months), investigators found frequent hyperglycemia (21% of patients), hyperinsulinemia (71%), hyperleptinemia (57%), hypertriglyceridemia (62%), and hypercholesterolemia (85%) (13). Internists should be on the alert for weight gain, diabetes, and other metabolic disturbances in patients receiving the newer antipsychotics.

New Therapeutic Developments

Transcranial Magnetic Stimulation and Vagus-Nerve Stimulation Provide Hope for Patients with Treatment-Resistant Depression

Patients often ask about new developments in treatment before their physicians may be aware of them. Two new treatments for depression are noteworthy: transcranial magnetic stimulation and vagus-nerve stimulation.

Klein E, Kreinin I, Chistyakov A, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. Arch Gen Psychiatry. 1999;56:315-20. [PMID: 10197825]

Transcranial magnetic stimulation shows promise in treating some psychiatric conditions (14). This procedure involves placing an electromagnetic coil on the scalp and passing a high-intensity current through the coil; the current is turned on and off rapidly, similar to the process for magnetic resonance imaging. A magnetic field is generated, and if its intensity is sufficient, depolarization occurs in the area of the brain under the coils. Transcranial magnetic stimulation decreases logarithmically over distance; thus, the effects of the procedure are limited to structures in the brain within 2 cm of the surface. Unlike electroconvulsive therapy, transcranial magnetic stimulation is primarily an outpatient procedure that requires no anesthesia. It produces discomfort at the scalp site of stimulation and occasionally mild headache. Although studied for different psychiatric conditions, it shows the greatest promise in treating depression.

In a double-blind study, Klein and colleagues randomly assigned 70 patients to receive slow repetitive transcranial magnetic stimulation in the right prefrontal area or sham transcranial magnetic stimulation. A difference between the two treatments began to appear within 1 week, and by study end a significant difference was evident in a group × time interaction for both the Hamilton Depression Rating Scale and Montgomery–Asberg Depression Rating Scale ($P < 0.03$). Adverse effects were limited to discomfort due to facial muscle contractions (14%) and mild headache (9%).

In this study, low-frequency, repetitive transcranial magnetic stimulation over the right prefrontal area of the brain had short-term beneficial effects in patients with major depression. Caution is warranted in interpreting these results. The published studies of this treatment differ substantially in design and stimulus measures. This study used a low-frequency impulse rather than a higher-frequency impulse. Higher-frequency impulses deliver more energy and provide depolarization to a deeper and larger area, but they are associated with a greater seizure risk.

With direct marketing and intensive media coverage, new developments often reach our patients before they reach our publications. In the case of transcranial magnetic stimulation, the studies to date show promise for this procedure, but its efficacy, safety, and optimal techniques remain to be established. It is an experimental, not standard, treatment.

Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Biol Psychiatry. 2000;47:276-86. [PMID: 10686262]

Vagus-nerve stimulation has been used to treat medically refractory seizures in Europe since 1994 and in the United States since 1997 (the U.S. Food and Drug Administration approved the therapy for medically refractory partial-onset seizures). A total of 9000 patients have been treated worldwide. Vagus-nerve stimulation may have application for psychiatric disorders, particularly mood disorders. Several observations suggested that vagus-nerve stimulation might alleviate mood disorders: 1) Mood improved in patients with seizure disorders who received vagus-nerve stimulation, a finding not entirely explained by seizure reduction; 2) positron emission tomography of patients with seizure disorders treated with vagus-nerve stimulation shows changes in the brainstem, limbic system, and other areas of the central nervous system that are similar to changes seen with antidepressant therapy; 3) most anticonvulsants appear to have some mood-stabilizing effects; and 4) in animal models vagus-nerve stimulation activates neurotransmitters associated with antidepressant activity (norepinephrine, serotonin, γ-aminobutyric acid, and glutamate).

In Rush and colleagues' small study, 30 adult outpatients with nonpsychotic treatment-resistant depression ($n = 21$), bipolar I disorder ($n = 4$), or bipolar II disorder ($n = 5$) completed a 12-week, open, unblinded trial of vagus-nerve stimulation. The first 2 weeks were a recovery period (no stimulation), followed by 10 weeks of vagus-nerve stimulation (2 weeks of vagus-nerve stimulation adjustment and 8 weeks of fixed-dose vagus-nerve stimulation). These patients were receiving a stable medication regimen and had not responded to at least two full medication trials or electroconvulsive therapy in their current depressive episode.

Response rates were 40% on the Hamilton Depression Rating Scale and Clinical Global Impression–Improvement scale and 50% on the Montgomery–Asberg Depression Rating Scale. Of the responders, 12 (25%) had ratings on the Medical Outcomes Study Short-Form 36 emotional subscale similar to those of the general population.

Hoarseness was the most common adverse effect. Throat pain, cough, and dyspnea may also occur. These symptoms are usually alleviated by adjusting vagus-nerve stimulation early in treatment. Although not reported in this trial or any epilepsy studies, postmarketing surveillance has reported six cases of asystole during the lead test while implanting the vagal-nerve stimulation device.

Of note, however, no cardiac events have occurred outside the implantation procedure.

This was a small, open, uncontrolled trial, and placebo effects could be powerful. Patients or families may ask about vagus-nerve stimulation after learning about it through media coverage or the Internet. They can be told it is still an investigational procedure and is being studied only in patients with severe, treatment-refractory mood disorders. A multisite randomized, controlled trial is under way.

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A Current Perspective of Suicide and Attempted Suicide

J. John Mann, MD

Suicide and suicide attempts are a major cause of death and morbidity worldwide. Suicide is generally a complication of a psychiatric disorder, but it requires additional risk factors because most psychiatric patients never attempt suicide. This review includes a hypothesized stress–diathesis model, which has implications for detection of high-risk patients and treatment interventions, and discusses promising treatment approaches that have been recently identified.

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Suicide, the eighth leading cause of death in the United States, accounts for more than 30 000 deaths per year. The total number of suicides has changed little over time. For example, 27 596 U.S. suicides occurred in 1981, and 30 575 occurred in 1998. Between 1981 and 1998, the age-adjusted suicide rate decreased by 9.3%—from 11.49 suicides per 100 000 persons to 10.42 suicides per 100 000 persons (www.cdc.gov/ncipc/wisqars). The suicide rate in men (18.7 suicides per 100 000 men in 1998) is more than four times that in women (4.4 suicides per 100 000 women in 1998). In females, suicide rates remain relatively constant beginning in the midteens. In males, suicide rates are stable from the late teenage years until the late 70s, when the rate increases substantially (to 41 suicides per 100 000 persons annually in men 75 to 84 years of age). White men have a twofold higher risk for suicide compared with African-American men (20.2 vs. 10.9 suicides, respectively, each year per 100 000 men). The risk in white women is double that of women in U.S. nonwhite ethnic/racial minority groups (4.9 vs. 2.4 per 100 000 women each year).

In countries other than the United States, the most recently reported rates of suicide vary widely, ranging from less than 1 in 100 000 persons per year in Syria, Egypt, and Lebanon to more than 40 in 100 000 persons per year in many former Soviet republics (www.who.int/whosis). Over the past century, Hungary had the world's highest reported rate of suicide; the reason is unknown. Of note, the reported rates of suicide in first-generation immigrants to Australia tend to be more similar to rates in their native country than to rates in their country of current residence (1, 2); these figures indicate the influence of culture and ethnicity on suicide rates.

Suicide is the third leading cause of death in persons 15 to 34 years of age. The U.S. suicide rate in all youths decreased by 18% from 1990 to 1998 (www.cdc.gov/ncipc/wisqars) despite a 3.6-fold increase from 1992 to 1995 in white men, a 4.7-fold increase in African-American men, and a 2.1-fold increase in African-American women. Worldwide, from 1950 to 1995 in persons of all ages, suicide rates increased by approximately 35% in men and only approximately 10% in women (www.who.int/whosis). The reasons for the differences in rates among age, sex, and ethnic groups and the change in rates since the 1950s are unknown.

Suicide is generally a complication of a psychiatric disorder. More than 90% of suicide victims have a diagnosable psychiatric illness (3–7), and most persons who attempt suicide have a psychiatric disorder. The most common psychiatric conditions associated with suicide or serious suicide attempt are mood disorders (3–8).

Investigators have proposed many models to explain or predict suicide (9). One such explanatory and predictive model is the stress–diathesis model (10). One stressor is almost invariably the onset or acute worsening of a psychiatric disorder, but other types of stressors, such as a psychosocial crisis, can also contribute. The diathesis for suicidal behavior includes a combination of factors, such as sex, religion, familial and genetic components, childhood experiences, psychosocial support system, availability of highly lethal suicide methods, and various other factors, including cholesterol level. In this review, I describe the neurobiological correlates of the stressors and the diathesis. Literature for this review came from searches of the MEDLINE database (1996 to the present) and from literature cited in review articles. The factors that determined inclusion in this review were superiority of research design (use of psychiatric controls, quality of psychometrics, diagnostic information on the study sample, and definition of suicidal behavior;

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prospective studies were favored), adequate representation of major points of view, and pivotal reviews of key subjects.

WHAT IS SUICIDAL BEHAVIOR?

Suicidal behavior refers to the most "clear-cut" and unambiguous act of completed suicide but also includes a heterogeneous spectrum of suicide attempts that range from highly lethal attempts (in which survival is the result of good fortune) to low-lethality attempts that occur in the context of a social crisis and contain a strong element of an appeal for help (11). Suicidal ideation without action is more common than suicidal behavior (11). In most countries, men have a higher reported rate of completed suicide, whereas women have a higher rate of attempted suicide (12). Men tend to use means that are more lethal, plan the suicide attempt more carefully, and avoid detection. In contrast, women tend to use less lethal means of suicide, which carry a higher chance of survival, and they more commonly express an appeal for help by conducting the attempt in a manner that favors discovery and rescue (13, 14). Thus, suicidal behavior has two dimensions (13). The first dimension is the degree of medical lethality or damage resulting from the suicide attempt. The second dimension relates to suicidal intent and measures the degree of preparation, the desire to die versus the desire to live, and the chances of discovery. Intent and lethality are correlated with each other and with biological abnormalities associated with suicide risk (13, 15, 16). The clinical profiles of suicide attempts and completions overlap (17). Suicide "attempters" who survive very lethal attempts, which are known as failed suicides, have the same clinical and psychosocial profile as suicide "completers" (11, 17). The study and prevention of failed suicides are probably most relevant to completed suicides.

Somewhat related to suicide attempters are patients with serious medical illnesses who do not adhere to treatment regimens—for example, diabetic patients who do not take prescribed medications to control blood sugar levels or persons who engage in high-risk behaviors, such as sky diving or mountaineering. These groups warrant further study to determine whether they have psychopathology that overlaps with the psychopathology of suicide attempters. Intent and lethality are also related to the risk for future completed suicide (13). Subsequent suicide attempts may involve a greater degree of intent and lethality (18), and a previous suicide attempt is an important predictor of future suicide (19, 20) or suicide attempt (21). Careful inquiry about past suicide attempts is an essential part of risk assessment in psychiatric patients. Because more than two thirds of suicides occur with the first attempt, history of a suicide attempt is insufficient to predict most suicides; additional risk factors must be considered.

CLINICAL CORRELATES OF SUICIDAL BEHAVIOR

Psychological autopsy studies involve review of all available medical records and interviews with family members and friends of the deceased. This method generates valid psychiatric diagnoses (22), and most studies have found that more than 90% of suicide victims had a psychiatric disorder at the time of suicide (3–6, 23). That percentage may be underestimated because accurate data depend on finding informants who knew the victim's state of mind in the weeks before death. Approximately 60% of all suicides occur in persons with a mood disorder (3, 4, 6, 7), and the rest occur in persons with various other psychiatric conditions, including schizophrenia; alcoholism (24); substance abuse (5, 25, 26); and personality disorders (27), such as borderline or antisocial personality disorder (23, 28–30). Lifetime mortality from suicide in discharged hospital populations is approximately 20% in persons with bipolar disorder (manic depression), 15% in persons with unipolar depression, 10% in persons with schizophrenia, 18% in persons with alcoholism, and 5% to 10% in persons with both borderline and antisocial personality disorders (29–33). These personality disorders are characterized by emotional ability, aggression, and impulsivity. The lifetime mortality due to suicide is lower in general psychiatric populations (34, 35). Although suicide is generally a complication of a psychiatric disorder, most persons with a psychiatric disorder never attempt suicide. Even the higher-risk groups, such as persons with unipolar or bipolar mood disorders, have a lifetime suicide attempt rate less than 50%. Thus, persons with these psychiatric disorders who die by suicide differ from those who never attempt suicide.

To understand those differences, investigators have compared persons who have attempted suicide and those who have not by matching psychiatric diagnosis and comparable objective severity of illness (10). Suicide attempters differ in two important ways from nonattempters with the same psychiatric disorder. First, they experience more subjective depression and hopelessness and, in particular, have more severe suicidal ideation. They also perceive fewer reasons for living despite having the same objective severity of psychiatric illness and a similar number of adverse life events. One possible explanation for the greater sense of hopelessness and greater number of suicidal ideations is a predisposition for such feelings in the face of illness or other life stressor. The pressure of greater lifetime aggressivity and impulsivity suggests a second diathesis element in suicidal patients. These individuals not only are more aggressive toward others and their environment but are more impulsive in other ways that involve, for example, relationships or personal decisions about a job or purchases. A propensity for more severe suicidal ideation and a greater likelihood of acting on powerful feelings combine to place some patients at greater risk for suicide attempts than others. For clinicians, important indicators of such a diathesis are a history of a suicide attempt, which indicates the presence of a diathesis for suicidal behavior, and a family history of suicidal behavior. Suicidal behavior is known to be transmitted within families, and the presence of a family history indicates the potential for transmission of both a psychiatric illness that generates suicidal ideation and a diathesis for suicidal behavior.

Other clinical features that increase the risk for suicidal behavior include comorbid substance abuse and alcoholism (5, 24, 25, 33, 34, 36–39), a history of physical or sexual abuse during childhood (40), a history of a head injury or neurologic disorder (41–45), and cigarette smoking (10, 46–49). Studies have reported a relationship between cigarette smoking and major depression that may contribute to the risk for suicide (48, 49).

Aggressive–impulsive traits, alcoholism and substance abuse, depression, and cigarette smoking all appear related to suicidal risk (47, 50–53). In addition, head injuries occur more frequently in persons with aggression and impulsivity and persons with alcoholism or substance abuse. This relationship is bi-directional because alcoholism, substance abuse, and aggressive behaviors sometimes follow head injuries (54–58). The greater frequency of aggressive behaviors and alcoholism in men (10, 24, 26, 59) may partly explain the higher suicide rates reported in men than in women.

FAMILIAL AND GENETIC FACTORS IN SUICIDAL BEHAVIOR

Persons who attempt or commit suicide have a significantly increased reported rate of suicidal acts in their families (60). Twin studies have shown a high concordance rate for suicides (61) and for suicide attempts (62) in monozygotic versus dizygotic twins. Adoption studies (63) have shown a higher reported rate of suicide in the biological parents of adoptees who commit suicide than in biological relatives of control adoptees. This relationship holds true even after adjustment for rates of psychoses and mood disorders. Studies of familial transmission indicate that the parents of youth suicide victims have higher rates of suicidal behavior independent of the presence of psychopathology (64). In summary, the heritability of suicide is comparable to the heritability of other major psychiatric disorders, such as bipolar disorder and schizophrenia.

The specific genetic factors that contribute to this risk, independent of the genetic factors involved in psychiatric disorders themselves, remain unknown. In association and linkage studies, researchers have identified candidate genes linked to suicidal behavior, including the gene for tryptophan hydroxylase (the rate-limiting biosynthetic enzyme for serotonin) and the serotonin 5-HT_{2A} receptor gene. Such studies have reported promising associations between an intronic polymorphism in the tryptophan hydroxylase gene and suicide attempt behavior and lower serotonergic function (65); however, the results from these types of studies are often unreliable.

Nongenetic familial factors that may contribute to suicide risk include the effect of parenting (40), physical or sexual abuse—possibly due to greater parental impulsivity and other psychiatric disorders, including alcoholism and substance abuse, that contribute to adverse parenting. The effect of modeling of suicidal behavior in important family members may also increase the risk for future suicidal behavior in children.

MEDICAL ILLNESSES AND SUICIDE RISK

Compared with the risk of the general population, persons with a potentially fatal illnesses, such as cancer, have only a relatively modest two- to fourfold increased risk for suicide, unless they have a comorbid psychiatric disorder (66). In contrast, disorders of the central nervous system—such as epilepsy (41, 42), AIDS (67), Huntington disease (43, 44), head injury (68), and cerebrovascular accidents (68)—carry a much higher relative risk for suicide. Pathology involving the brain may trigger depression and suicidal ideation and may impair restraint or inhibition of the desire to act on such thoughts (54, 55, 57, 58, 68, 69). This dual effect may explain the greater relative risk associated with central nervous system abnormality compared with diseases of other systems.

PSYCHOSOCIAL AND OTHER ENVIRONMENTAL CORRELATES OF SUICIDAL BEHAVIOR

Rural areas, high rates of gun ownership, poverty, unemployment, and social isolation have all been implicated in suicide (70, 71). How important these factors are by themselves is unknown. Because psychiatric disorders can lead to a decrease in socioeconomic status, the breakup of a marriage or significant relationship, or the failure to form meaningful relationships, separating the effect of psychosocial adversity from that of psychiatric illnesses can be difficult. Psychiatric illness can lead to psychosocial adversity, and both factors can combine to increase the person's level of stress and thereby potentially increase the risk for suicidal behavior.

AVAILABILITY OF THE MEANS FOR SUICIDE AND THE RISK FOR SUICIDE

The availability of highly lethal suicide methods and rates of suicide appear to be related (72, 73). Reported suicide rates of more than 100/100 000 persons each year in rural China and Sri Lanka partly result from the availability of highly lethal methods for suicide, such as pesticides. The rate of suicide attempts is generally approximately 10 times higher than the rate of completed suicide. This means that approximately 1 in 10 suicide attempts ends in death. When generally fatal methods for suicide are used, the rate of completed suicide approaches the rate of attempted suicide. This may be the case in rural Sri Lanka and China, where suicide rates are 10- to 20-fold higher than in most countries and where the suicide rate in women exceeds that in men. Removing or reducing access to highly lethal methods of suicide can transiently reduce suicide rates. This was successfully demonstrated in Japan after carbon monoxide was removed from coal gas (74) and may also be possible through gun control (72, 75).

There is debate about the relation between availability of guns and risk for suicide (76). According to a search of the MEDLINE database, 10 studies have shown that a gun in the house, even if it is unloaded, increases the risk for suicide in adults and youths (77), and only 1 study disagreed (71). U.S. cities with strict laws on gun control and gun ownership appear to have lower rates of suicide in the home by gunshot (78). The significant increase in youth suicide that has principally involved men younger than 45 years of age parallels an increase in suicide by using guns (72). Investigators have postulated that, in general, the more difficult it is to access highly lethal methods of suicide, the more likely the person is to use a less lethal method and therefore the greater the likelihood of survival. Thus, gun control may not influence the rate of suicide attempts, but it may influence the rate of survival from suicide. The use of new-generation antidepressant medications, such as selective serotonin reuptake inhibitors, is associated with no difference in suicide attempt rates compared with tricyclic antidepressants but a higher survival rate in the event of an overdose with these agents (79). The completed suicide rate, relative to the rate of attempts, may be lower if access to more lethal methods of suicide is reduced.

IMITATION SUICIDE AND SUICIDE IN THE MEDIA

Glamorous portrayal of suicides in the electronic or print media carries the risk for imitation or copycat suicides (80). Following each of the two airings (1 year apart) of a German television series involving a young person committing suicide by jumping in front of a high-speed train, the number of youth suicides in Germany involving high-speed trains increased (81). Similar increases in youth suicide following highly publicized suicides have been reported in the United States (80, 82, 83). A book by Goethe involving the suicide of a young man called Werther resulted in a spate of suicides in Europe and led to the banning of the novel from several countries (81). To reduce future occurrences of this so-called Werther effect, the media now have guidelines about avoiding glamorization of suicide and educating the public on the association between suicide psychiatric illness and the availability of effective forms of help.

NEUROBIOLOGY OF SUICIDAL BEHAVIOR

Numerous studies have shown that altered serotonergic function is associated with the diathesis for suicidal behavior (84). Postmortem brain receptor mapping studies (85, 86) suggest that reduced serotonergic input to the orbital prefrontal cortex, an area of the brain involved in behavioral inhibition, may be deficient in persons who are at risk for suicidal behavior and may underlie a general propensity for aggressive and impulsive behaviors. Serotonergic hypofunction appears to be associated with more lethal suicidal behavior (16, 87). Moreover, serotonin receptor populations are altered in the brains of suicide victims. Brain dysfunction in suicidal persons is suggested by decreases in presynaptic binding sites in the prefrontal cortex—for example, lack of serotonin transporter binding on serotonin nerve terminals—and by the increases in postsynaptic receptors—such as the 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors— that have been demonstrated in some but not all studies (88). These quantitative changes in receptors, together with lower levels of serotonin or its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in the brainstem of suicide victims, are associated with suicide independent of the primary psychiatric diagnosis (88). Cerebrospinal fluid levels of 5-HIAA are lower in persons who have made serious suicide attempts than in psychiatrically matched controls; this effect is also independent of psychiatric diagnosis and is present in persons with mood disorders, schizophrenia, or personality disorders who have made serious suicide attempts. Low serotonergic function may be a trait marker of suicide potential, and this observation is supported by the fact that low cerebrospinal fluid levels of 5-HIAA predict future suicide and suicide attempts in psychiatric patients with mood disorders or schizophrenia (89–91).

The observation that there is a genetic component involved in suicide risk raises the question of how genetic factors can influence suicide risk. Because some genetic factors regulate serotonergic function, it has been suggested that genetic factors can influence suicide risk by affecting serotonergic function (65). Candidate gene studies are testing this hypothesis.

Recent evidence has linked reduction of cholesterol levels by drugs or diet, as well as spontaneously occurring very low levels of cholesterol, to suicide risk (92, 93). A very small increase in the rate of suicide and perhaps suicide attempts and ideation is reported in persons with very low cholesterol levels (94). In nonhuman primates, a low cholesterol diet is associated with lower serotonergic activity and increased aggressive behaviors (93, 95). Although this relationship has not yet been demonstrated in humans, it may explain how cholesterol levels can influence suicide risk. Suicide—and also accidental deaths—increases with decreasing cholesterol levels (93, 94). This effect may be greater in cholesterol reduction by diet than in reduction by 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitor therapy (94). In practical terms, the effect of cholesterol level on the risk for suicide is extremely small and of no use as a predictive test.

Studies of the noradrenergic system indicate that there are fewer noradrenergic neurons in the locus ceruleus of suicide victims (96) and increased brainstem levels of tyrosine hydroxylase and lower levels of postsynaptic adrenergic receptors in the cortex (97). This picture may also be explained by an increased stress response before suicide, resulting in the excessive release of norepinephrine and a secondary upregulation in tyrosine hydroxylase biosynthetic activity and a downregulation of postsynaptic adrenergic receptors in the cortex. In addition, corticotropin-releasing hormone binding is reportedly reduced in the prefrontal cortex of suicide victims, and this may reflect increased release of corticotropin-releasing hormone (98). This may be a stress response (99) or may occur in association with a hyperactive hypothalamic–pituitary–adrenal axis, an effect reported in major depression (100) or future suicide (101). Severe anxiety or agitation is associated with suicide risk (102) and hypothalamic–pituitary–adrenal overactivity (103).

These findings highlight the importance of distinguishing among the neurobiological changes associated with a primary psychiatric disorder, such as major depression or psychosis, the neurobiological abnormalities related to the diathesis for suicidal behavior, and the neurobiological manifestations of excessive stress, which many patients experience in the period leading up to their suicide. The use of brain imaging and other methods to assess this biological vulnerability may some day help clinicians evaluate the suicidal patient.

ASSESSMENT AND MANAGEMENT OF THE SUICIDAL PATIENT

It is estimated that 50% of persons who commit suicide had sought professional help within 1 month of the act (104), affording an opportunity for prevention. On the Swedish island of Gotland, education of general practitioners in the recognition and treatment of depression in 1983 was associated with increased antidepressant prescriptions and a decrease in the annual suicide rate from 20 suicides per 100 000 residents in 1983 to 7 suicides per 100 000 residents in 1985—the lowest ever recorded in Gotland (105). None of the seven suicide victims in 1983 had been under the sole care of a general practitioner, indicating a need for public education to supplement physician education. The high level of medical contact before suicide means that effective preventive treatment interventions are possible (106).

The management of the suicidal patient involves three major components (107): 1) diagnosis and treatment of existing psychiatric disorders, 2) assessment of suicide risk, and 3) removal of the means for suicide and specific treatment to reduce the diathesis or propensity to attempt suicide.

Suicidal patients generally present in one of two ways: 1) with a psychiatric disorder for which they seek treatment or 2) particularly with mood or anxiety disorders, with a medical problem that brings the patient to either their general practitioner or internist. Careful assessment of symptoms such as depressed mood, hopelessness, guilt, insomnia, tiredness, anorexia, weight loss, constipation, and poor concentration can indicate major depression and not an occult neoplasia. Effective treatment of major depression is critical because less than 1 in 6 patients who commit suicide during a major depressive episode are receiving adequate dosages of antidepressant medication (108). Thus, more effective recognition and treatment of depressive illness may substantially reduce suicide rates (109). This strategy may work in the United States, where most persons with a depressive illness (including those with a history of a suicide attempt) are not receiving antidepressant treatment (110).

Some patients seek help—often by presenting to an emergency department—after a suicide attempt involving methods with a low level of lethality. The low lethality of the presenting suicide attempt should not lead to the conclusion that the potential for more serious suicide attempts or completed suicide is low. Careful psychiatric evaluation, including a history of past suicidal behavior, may reveal more lethal suicide attempts. Comorbid alcoholism or substance abuse significantly increases the risk for suicide in persons with a mood disorder (52) or schizophrenia (111). Appropriate management and treatment of these psychiatric disorders should be initiated.

The best predictor of suicidal behavior is a history of a suicide attempt and current suicidal ideation. The association of suicidal ideation and action is stronger in the short term rather than in the long term (112, 113). Suicidal ideation that includes a plan for suicide or evidence that the individual has been engaging in preparations for a suicide attempt are serious signs of short-term risk. Suicidal men are half as likely as suicidal women to report suicidal ideation to their physician before suicide (114). It is best to actively elicit such information. Available relatives can sometimes provide additional information about behaviors that indicate planning a suicide attempt or statements from the patient that suggest a specific plan. Clinicians should systematically inquire about current depression, hopelessness, and suicidal ideation, in that order. Depending on the presence of a plan for suicidal behavior or the severity of the suicidal ideation, the patient may require observation up to and including admission to hospital. In at-risk patients, the availability of a means for suicide should be reduced and, in particular, guns should be removed from the house. The cornerstones of management are the treatment of the associated psychiatric disorder; the improvement of the psychosocial support system for the patient, including psychoeducation for the family; and careful observation and separation from the means for suicide, which may require hospitalization.

Scientific evidence about the specific treatments beneficial for suicidal behavior (rather than the psychiatric condition that is being treated) is lacking. However, recent evidence has shown that lithium used as a mood stabilizer may have specific antisuicidal properties beyond its mood-stabilizing effects in patients with bipolar disorder and in unipolar patients with recurrent depressions (115, 116). Lithium is used to prevent the recurrence of manic or depressive episodes in these conditions, but it also appears to significantly reduce the risk for suicide and suicide attempts. Discontinuation of lithium therapy increases suicidal behaviors and therefore should be done gradually (over a period of weeks) to reduce the chances of a recrudescence of suicidal behavior. The antisuicidal effect of lithium is striking because of the potential toxicitiy of the drug on overdose; this suggests that lithium must also decrease the number of suicide attempts, and retrospective data support this conclusion (115). The antisuicidal effects of anticonvulsant mood stabilizers remain to be tested. In schizophrenia, evidence shows that the atypical antipsychotic clozapine may reduce suicidal behavior independent of its therapeutic advantages as an antipsychotic agent (117–119). Data on the antisuicidal effects of other atypical antipsychotics would be of great interest given their favorable side effect and toxicity profiles. The mechanisms by which lithium and clozapine may have additional antisuicidal therapeutic effects are unknown, but there appears to be a potential for altering the diathesis for suicidal behavior. Both agents have pronounced effects on the serotonergic system that has been shown in neurobiological studies to be associated with the diathesis for suicidal behavior. Perhaps these two medications somehow alter serotonergic function in a way that reduces the diathesis for suicidal acts. This hypothesis requires formal testing.

CONCLUSIONS

Suicide is a complication of psychiatric disorders. The probability of suicidal behavior also depends on a diathesis that includes hopelessness and increased lifetime impulsivity that may be related to a specific impairment of serotonergic input into the ventral prefrontal cortex. The management of suicidal behavior involves an assessment of risk, the treatment of the primary associated psychiatric disorder, and the reduction of access to highly lethal methods for committing suicide, such as guns.

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Legal, Financial, and Public Health Consequences of HIV Contamination of Blood and Blood Products in the 1980s and 1990s

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Ensuring the safety of the blood supply connects politics and science. The business and service sectors share responsibility for the collection and processing of blood donations, and government agencies perform regulatory and surveillance roles. The onset of the AIDS epidemic has challenged the interface among these systems, leading to widespread fears about compromised safety of the blood supply. Because of public concern about blood-supply decisions made in the 1980s, developed countries in the 1990s established reimbursement programs for persons with transfusion-acquired viral infections from blood or blood products, adopted diagnostic tests and procedures that improved the safety of the blood supply, and held criminal judicial investigations of government officials and industry leaders accused of delaying implementation of potential blood-safety measures. In contrast, developing countries continue to struggle with blood-supply safety issues. This paper summarizes the current status of these safety concerns in developed countries, where viral transmission from contaminated blood or blood products is extremely rare, and in developing countries, where up to 10% of HIV infections result from transfusion of blood or blood products.

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During the onset of the AIDS epidemic in 1981, persons with hemophilia and blood-transfusion recipients throughout the world became infected with HIV through transfusion of contaminated blood products (1–7) (Table 1). In 1982, 1 year after the first AIDS cases were reported, the U.S. Centers for Disease Control and Prevention suggested that the syndrome was associated with blood and blood products (11, 12).

Several developed countries have recently completed criminal investigations, civil litigation, and monetary financing programs to deal with the compromised safety of the blood supply during the first decade of the AIDS epidemic. In contrast, developing countries face continued concerns about the safety of their blood supplies. We review the current status of blood-supply considerations in several developed and developing countries.

CRIMINAL INVESTIGATIONS

In France in 1992, Michel Garretta, former head of the National Blood Transfusion Center, and Jean-Pierre Allain, former head of research at the Center, were sentenced to prison for supplying HIV-infected clotting factors to hemophiliac patients (Table 2). Garretta and Allain were accused of having major roles in the National Blood Transfusion Center's decision not to use heated blood products after 1983—an action purportedly taken because of a belief that the French blood supply was safe. From 1983 to 1985, policymakers did not require that blood donors be routinely questioned about drug use and homosexual experiences. Because of a desire to use only domestically obtained blood products, prisoners became a major source of blood products from 1983 to 1985, even though other countries, such as Finland and Canada, had discontinued this practice in the 1970s. Jacques Roux, the former director general of the Health Ministry, received a suspended sentence for his part in these actions. The French scientific community and 30 Nobel Prize winners petitioned for pardons of Garreta, Allain, and Roux (13–15). Controversy also surrounded French approval of the HIV enzyme-linked immunosorbent assay (ELISA). Although the ELISA manufactured by Abbott Laboratories (North Chicago, Illinois) was approved in the United States in March 1985 and was presented for approval in France in February 1985, the French National Public Health Laboratory ruled in favor of the ELISA from the Institut Pasteur in June 1985, reportedly because of economic considerations (16–19). The former Prime Minister, the Secretary of State for Health, and the Minister of Social Affairs were criminally charged with delaying the application. Public unrest, particularly among persons with hemophilia, led to court trials without convictions in 1994 and retrials in 1998 (20–23). Of the three officials charged, only the former Secretary of State for Health was convicted (of manslaughter), but he received no penalty.

Criminal investigations in Germany led to convictions of five officials of UB Plasma in Koblenz for inflicting bodily harm from 1987 to 1993 by selling thou-

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sands of units of viral-infected blood products that were inconsistently tested for HIV (23). In 1993, Germany's health minister recommended HIV testing of persons who had received blood transfusions in the 1980s, fueling speculation of a cover-up. Afterward, Haemoplas, a German blood products company, was charged with having inconsistently tested for HIV in 1986 and 1987. Two officials were charged with murder, and one was sentenced to 6.5 years in prison (24–26).

In 1973, the New York Blood Center established a relationship with the Swiss Red Cross, which had a history of innovation and professionalism. As a result, the Center began importing its blood supply from Switzerland (8). In 1985, using ELISA, the Center detected HIV in imported Swiss blood products (27). Alfred Haessig, former director of the Swiss Red Cross's Central Laboratory, was given a suspended sentence in 1998 for delaying introduction of donor screening questionnaires until May 1986, maintaining that HIV could be chemically inactivated, delaying use of imported heat-treated blood products, and testing only exported blood products for HIV (8, 28).

In 1996, Dr. Takeshi Abe, the former head of the Japanese AIDS Study Group, was charged with negligence in the death of a patient with hemophilia (29, 30). In 1983, Dr. Abe led a task force that allowed importation of untreated blood products. He was a prominent leader of hemophilia home treatment after government approval of reimbursement for factor VIII concentrate. In 1984, the National Institutes of Health found that 23 of 48 blood samples from Japanese persons with hemophilia were HIV infected (30). Dr. Abe reported this to the Japanese Health and Welfare Ministry but not patients or the public. A high percentage of a second set of blood samples also tested positive for HIV, but Dr. Abe again did not notify the public. As late as 1988, Dr. Abe and other hemophilia specialists did not inform patients that they were HIV positive, reportedly because they believed that since curative therapy for AIDS was lacking, there was no need to inform individuals about their HIV status. In 1989, legislation finally required notifying patients if they had AIDS (31). Factors that had contributed to poor decision making included statements by Japanese hemophilia specialists in 1983 that AIDS was not a Japanese problem and in 1985 that unheated factor VIII products imported from the United States were safe and constantly improving in quality; another factor was delayed adoption of heat-treated products due to concern that this would allow market dominance by Baxter Healthcare Corp. (Deerfield, Illinois). In 2000, Takehiko Kawano, former president of the Green Cross Corp. (Osaka, Japan), and two predecessors were sentenced to 16 to 24 months in prison for having sold non–heat-treated blood products in 1986 and for not recalling these products until 1988 (32–35). Akihito Matsumura, a former official in the Japanese Ministry of Health and Welfare, was indicted in 1996 and ultimately found guilty for perpetuating the spread of HIV through the blood supply (34). From 1983 to 1985, Japan accounted for one third of the world's annual use of plasma products, 90% of which were imported from the United States (35).

Table 1. **Persons with Hemophilia Who Developed HIV Infection from Transfusion of Contaminated Blood Products in Selected Countries***

Country	Persons with Hemophilia Who Became Infected, *n* (%)
United Kingdom	1700 (32)
Japan	1800 (45)
France	2000 (50)
United States	10 000 (50)
Canada	800 (55)†
Denmark	210 (64)‡§

* Except where otherwise noted, data in the table were obtained from Starr (8).
† Data obtained from Kondro (9).
‡ Data obtained from Feldman and Bayer (10).
§ Approximate number.

In Canada, Justice Horace Krever chaired the Commission of Inquiry on the Blood System, which began hearings in February 1994 and released its final report in March 1997. The report had four major findings: 1) Many blood safety problems resulted from poor coordination among organizations responsible for the blood system; 2) urgency in the provision of heat-treated factor concentrate had been lacking; 3) the 8-month delay between the time that the United States had approved an HIV ELISA in March 1985 and when Canada approved the test in November 1985 had resulted in HIV infection in many recipients of blood and blood products during this period; and 4) physicians and the general population had not been informed about AIDS and hepatitis risks (36, 37). Subsequently, the blood supply responsibilities of the Canadian Red Cross were eliminated and a new agency, the Canadian Blood Services, was charged with these responsibilities (38–42).

Table 2. **Individuals Criminally Indicted for Blood-Supply Safety Concerns**

Country	Persons Charged	Affiliation	Charge	Year of Indictment	Court Decision
France	Michel Garretta	Former head, National Blood Transfusion Center	Poisoning in 1983–1985	1991	Convicted in 1992
	Jean-Pierre Allain	Former research chief, National Blood Transfusion Center	Poisoning in 1983–1985	1991	Convicted in 1992
	Jacques Roux	Former director general, Health Ministry	Poisoning in 1983–1985	1991	Convicted in 1992
	Robert Netter	Former director, National Health Laboratory	Poisoning in 1983–1985	1991	Acquitted in 1992
	Laurent Fabius	Former Prime Minister	Manslaughter in 1983–1985	1994 and 1998	Acquitted in 1999
	Edmond Hervé	Former Secretary of State for Health	Manslaughter in 1983–1985	1994 and 1998	Convicted in 1999; was never sentenced
	Georgina Dufoix	Former Minister of Social Affairs	Manslaughter in 1983–1985	1994 and 1998	Acquitted in 1999
Germany	Director and four staff members	UB Plasma Corp.	Inflicting bodily harm in 1987–1993	1994	Convicted in 1995
	Frank Giesbert and Günter Eckert	Haemoplas Corp.	Murder in 1986 and 1987	1995	Convicted in 1997
Switzerland	Alfred Haessig	Former director, Swiss Red Cross	Endangering the safety of patients with hemophilia in 1985 and 1986	1995	Convicted in 1998; received a 1-year suspended sentence
Japan	Takeshi Abe	Former head, government AIDS study group and chairman, internal medicine department of Teikyo University, Tokyo	Professional negligence leading to death in 1983–1988	1996	Acquitted in 2001
	Takehiko Kawano	President, Green Cross Corp.	Professional negligence leading to death in 1986–1988	1996	Convicted in 2000; sentenced to prison
	Renzo Matsushita	Former President, Green Cross Corp.	Professional negligence leading to death in 1986–1988	1996	Convicted in 2000; sentenced to prison
	Tadakazu Suyama	Former President, Green Cross Corp.	Professional negligence leading to death in 1986–1988	1996	Convicted in 2000; sentenced to prison
	Akihito Matsumura	Former official, Ministry of Health and Welfare	Knowingly perpetuating the spread of HIV infection through the blood supply in 1986–1988	1996	Convicted in 2000; received a 1-year suspended sentence

MONETARY COMPENSATION AND CIVIL LITIGATION

More than 20 countries have established compensation programs for persons infected with HIV as a result of HIV-contaminated blood products (43, 44). Funds have often been given to family members who were resultantly infected or to surviving family members of deceased persons who had been infected. To be eligible for monetary compensation, persons usually must renounce their civil rights to any future action against government entities. However, this stipulation has not prevented the filing of lawsuits against private institutions. In Canada, several suits were won against the Canadian Red Cross, which was found to have "failed utterly to provide the users of blood and blood products with authoritative, accurate and updated information" (45) (Table 3). In April 2001, the Canadian Supreme Court found the Canadian Red Cross guilty of negligence for failing to screen blood donors in the early 1980s, when the nation's blood supply became infected with the AIDS virus. The Supreme Court upheld a judgment by the Ontario court of appeal, which had said that the Red Cross failed to exercise a proper standard of care in its collection of blood. The ruling stems from three cases brought by blood recipients who received blood from the Canadian Red Cross Society between 1983 and 1985. Two of the plaintiffs died of AIDS complications, and the third is alive and is HIV positive (46). Armour Pharmaceutical Co., which was a division of Rhône-Poulenc Rorer Pharmaceuticals, Inc. (Paris, France), paid six Canadians with hemophilia $1.5 million each after discovery of a document indicating that some heat-treated products had not been fully deactivated in the mid-1980s (47). In Italy in 1998, a civil court ruled that the Ministry of Health was responsible for the consequences to patients who had received commercially available contaminated blood products in the 1980s. The Ministry of Health was found to have "omitted its duties of prudence, diligence, impartiality, and legality" in not recommending viral inactivation treatment for human plasma until 1985, not withdrawing products that were not subjected to this treatment until 1988, and not instituting systematic blood-donor screening until 1994. Overall, 80% of the human plasma products sold in Italy by foreign manufacturers in the 1980s were processed without proper quality control (48).

The United States was one of the last developed countries to compensate persons with hemophilia. In 1995, an Institute of Medicine report (5) indicated that many organizations shared the blame for compromised blood safety in the 1980s, including the Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), the National Institutes of Health, community blood banks, the American Red Cross, blood and plasma collection agencies, blood product manufacturers, and groups such as the National Hemophilia Foundation (5). The committee also reported that in 1983 and 1984, blood banks and fractionation companies should have initiated surrogate laboratory testing and should have excluded homosexual men from blood donation. In response, Thomas Zuck, a former FDA official, indicated that it was difficult to make decisions at that time given uncertainty about the estimates of risks to the blood supply (6). Before AIDS and during the period when hepatitis B had initially been a safety problem, policymakers concerned with international blood safety had operated under basic scientific principles, which held that policies were changed only after definitive results from empirical studies had been reported. There also was an international sense of obligation to voluntary donors and a reluctance to include questions about potential high-risk behaviors given the uncertainty about whether these behaviors caused AIDS. As a result of civil lawsuits, HIV-infected transfusion recipients have received an unascertainable amount of awards and financial settlements. Fractionation companies subsequently completed a financial settlement with the Committee of Ten Thousand—a group of 10 000 HIV-infected persons with hemophilia who had lobbied for the Institute of Medicine report. This settlement authorized payments of $100 000 to HIV-infected persons with hemophilia and to persons they had infected (49). In 1998, after years of lobbying by hemophilia organizations, Congress passed the Ricky Ray Hemophilia Relief Fund Act, which authorized $750 million to support payments to persons with hemophilia who had received HIV-infected clotting concentrate. Over $650 million has been appropriated by the Congress for the fund, and more than $205 million in compassionate payments has been committed (50).

MAINTAINING A SAFE BLOOD SUPPLY

Steps were taken to ensure the safety of the U.S. blood supply during the first two decades of the AIDS epidemic. Early improvements were cost-effective, including universal adoption of HIV antibody testing (cost, $3600 per quality-adjusted life-year saved) and alanine aminotransferase and hepatitis C virus (HCV) testing (which were cost-saving) (51). Recent interven-

Table 3. **Compensation Schemes from Seven Countries for Persons Infected with HIV from Blood or Blood Products***

Country	Annual Compensation		One-Time Compensation	
	Amount	How Funded	Amount	How Funded
United States	–		$100 000	Out-of-court settlement with plasma fractionators plus government fund
Germany	$10 656 for HIV $21 324 for AIDS	Government trust fund Government trust fund	–	
France	–		$263 204 $87 735 at the time of AIDS diagnosis	Government fund Government fund
Canada	$22 096	Government fund	$16 204 $176 640†	Government fund Government fund
Switzerland	$12 216 for AIDS	Government, plasma fractionators, and Swiss Red Cross	$84 838 (maximum amount)	Swiss Red Cross
Italy	To be determined	–	To be determined	–
Japan	–		$450 000	Settlement with the Ministry of Health and Welfare and plasma fractionators

* Compensation figures are expressed in 1998 U.S. dollars.
† For Canadians who contracted HIV from parents or partners originally infected through HIV-infected blood transfusions.

Table 4. **Crude and Adjusted Incidence of Seroconversion Associated with Each of Four Major Bloodborne Viruses***

Virus	Crude Incidence per 100 000 person-years	Adjusted Incidence per 100 000 person-years (95% CI)†
HIV	4.01	3.37 (2.22–4.76)
Human T-cell leukemia	1.09	1.12 (0.51–1.98)
Hepatitis C	4.84	4.32 (2.35–6.87)
Hepatitis B	9.54	9.80 (6.74–13.42)

* Adapted from reference 52.
† Adjustments to crude incidence rates accounted for seroconverters whose last donation before the one in which antibodies were detected could not be used—because it tested positive for another marker, such as elevated alanine aminotransferase levels, or because of confidential unit exclusion.

tions have been less cost-effective and more controversial. In 1996, the FDA approved an HIV P24 antigen assay (at a cost of $2 million per quality-adjusted life-year saved). Of 6 million donations tested in 1996, two were P24 antigen–positive but HIV antibody–negative. There is a controversial move towards universal leukoreduction of all nonleukocyte transfusion blood components, which is estimated to cost $600 million annually. This change may not prevent transmission of any virus, except cytomegalovirus, a common infection that poses a risk only to some immunocompromised patients.

In 1999 and 2000, more than 90% of the U.S. blood supply underwent nucleic acid amplification testing. During this testing, 16.3 million donations were evaluated for HCV RNA and 12.6 million were evaluated for HIV RNA. This testing detected 62 donations that were HCV RNA positive but serologically negative. Four donations were HIV RNA positive but serologically negative. Only one blood component that tested positive for HCV was transfused (52). Red blood cells have not been quarantined nationwide until such test results are known, seemingly because some shelf supplies have been insufficient to allow an additional 2 to 3 days of quarantine (53). Overall, testing of the blood supply costs $25 to $35 per unit, accounting for 13% to 20% of the total retail charge. In addition, recent blood-supply shortages have led to delays of surgeries; some blood centers have less than a 1-day supply of type O blood (54). Today, the rates of seroconversion among blood donors are 1 to 4 per 100 000 person-years for HIV, human T-cell leukemia virus, and HCV (**Table 4**) (55). Plasma concentrates are also very safe; all are heat treated, and some are exposed to solvent detergents (cost, $300 000 per quality-adjusted life-year saved) (51).

Because of concern over Creutzfeld–Jakob disease transmission, the FDA published a guidance in November 1999 recommending deferral of blood and plasma donors who had visited the United Kingdom for 6 months or longer between 1980 and 1996, a policy that eliminates 2.2% of otherwise qualified blood donors (56). The Transmissible Spongiform Encephalopathies Advisory Committee to the FDA published interim recommendations in August 2001 supporting deferral in 2001 of donors of all blood and blood components who had lived in the United Kingdom for 3 months or longer between 1980 and 1986 or who had lived 5 years or longer in France between 1980 and the present. The interim recommendations also supported deferral after October 2002 of blood donors, but not plasma donors, who had lived in Europe for 5 years or more between 1980 and the present (56).

Organizational changes and improvements in blood products oversight have occurred in the United States over the past 15 years. A centralized Blood Safety Committee and additional blood surveillance centers were authorized, and the FDA Blood Products Advisory Committee was advised to consider safety and efficacy, but not cost-effectiveness, in its decision making. Large organizations—including the New York Blood Center; the Red Cross in Los Angeles, California; United Blood Services in Tucson, Arizona; and two plasma-product companies, Centeon, LLC (originally a joint venture between Rhône-Poulenc Rorer, Inc., and Hoechst AG; now known as Aventis Behring, LLC; King of Prussia, Pennsylvania), and Alpha Therapeutic Corp. (formerly a U.S. subsidiary of Green Cross Corp., Osaka, Japan)—were issued federal consent decrees and have recalled blood products.

Policy changes have also been adopted in other countries. French transfusion centers are now controlled by a Transfusion Agency, which reports directly to the Minister of Health. Japan no longer imports factor VIII but still imports albumin and gammaglobulin. In 1998, a smaller pharmaceutical company, Yoshitomi Pharmaceutical Industries Ltd. (Osaka, Japan), took over Green Cross Corp. (55). The United Kingdom centralized its blood industry and completed work on a fractionation facility that provides almost 75% of the country's blood product. Many blood-supply policies in the United

Kingdom have been based on concerns about the prion-caused illnesses bovine spongiform encephalopathy and new-variant Creutzfeld–Jakob disease. Bovine spongiform encephalopathy contamination has affected almost 180 000 British cattle and 230 to 540 total cattle in Ireland, Portugal, Switzerland, and France (57, 58). Cases of new-variant Creutzfeld–Jakob disease have occurred in 88 persons in United Kingdom, 1 person in France, and 1 in Ireland, and a maximum epidemic size of 500 000 has been estimated. While new-variant Creutzfeld–Jakob disease has not been identified from recipients of blood from donors who eventually developed clinical Creutzfeld–Jakob disease, no diagnostic tests can screen for Creutzfeld–Jakob disease in the blood supply, and bovine spongiform encephalopathy theoretically can be transmitted through blood transfusions from persons who have eaten contaminated beef (59, 60). The British government has destroyed pooled plasma products from British blood donors; instead, Britain now uses pooled plasma products imported from the United States and has adopted a policy of universal leukoreduction of all other blood products from British donors. These blood-supply policies cost $165 million annually—half of the National Blood Service budget—and have adverse funding implications for other areas of the National Health Service.

DEVELOPING COUNTRIES

Blood safety continues to be a concern for developing countries, as up to 45% of donations in these countries are unscreened for HIV, HCV, or hepatitis B virus, and such donations account for hundreds of thousands of infections (61). A Red Cross Society blood bank in Bombay was closed in 1995 for supplying HIV-infected blood to hospitals between 1992 and 1994. Almost 9% of the 2574 cases of AIDS in India reported by 1996 were from transfusion recipients of HIV-infected blood or blood products, and 95% of the blood supply was estimated to be unsafe (62, 63). The government undertook extensive measures to improve blood safety, such as making HIV screening mandatory at all blood banks, banning professional blood donations, establishing National and State Blood Transfusion Councils to oversee all aspects of the blood safety program, and launching a program to modernize and strengthen the management of blood banks (63). Nonetheless, significant problems persist. The 3-year-old order by India's Supreme Court banning professional blood donations has worsened blood shortages and raised the cost of blood in the underground market. India's requirement of blood is estimated at 7.5 million units annually, while currently only 4 million units per year are collected. Blood screening practices continue to be poor. A survey of blood bank directors done in 2000 found that while 87% of respondents screened blood for hepatitis B virus and 95% for HIV, only 6% screened for HCV (64).

India plans to phase out paid donors, who have provided half of India's blood supply, and to revamp its 1400 blood banks, which are inadequately supplied (65). In Pakistan, a Red Cross consultant reported infrequent HIV testing of donated blood. In many parts of Southeast Asia, there is a market for blood donors (66). In 1990, 1 in 2644 blood donations in Thailand came from donors in the window period between HIV infection of such donors and the time when their viral levels are first detectable (67). That number has decreased, but levels of HIV infection in Thai donors are still high. In Vietnam, the director of the Central Haemotology and Blood Transfusion Institute announced in 1997 that 100 persons contracted HIV infection through blood transfusions. Paid professionals made up 80% of the blood donors in Vietnam, and although all blood was screened for HIV, professional donors had high rates of donations in the HIV window period (68). In the late 1990s, Ethiopia received screening equipment but lacked trained staff to operate such equipment (69).

China faces one of the most severe HIV-related blood-supply problems today. In the 1980s, paid blood donors with HIV infection introduced the virus into China. Because Chinese culture considers blood sacred, donors, who earn about $250 for donations of 1 to 2 units, have been the primary source of blood in China for several decades. In 1993, the demand for blood expanded as the Health Minister at that time, Chen Mingzhan, approved a plan to export blood products. Middlemen, called "blood heads," purchased blood from farmers and sold the blood to hospitals, blood banks, and blood-product suppliers. In 1994, tests of units of blood from Guan County, near Beijing, provided the first evidence that HIV-infected persons were donating blood. In 1995 and 1998, the National People's Congress passed laws to stop the selling of blood and to re-establish a voluntary donation system to improve blood supply safety (70). Despite these laws, paid donors continue to supply 60% of the country's blood donations (71). Testing of the blood supply for HIV, although mandated, has been infrequent. Moreover, the donation process often results in HIV infection through re-use of needles, mixing of blood products while obtaining plasma from several donors simultaneously, and reinfusion of HIV-infected blood to donors in an effort to reduce the time between donations. Hundreds of thousands of the 600 000 HIV-infected persons in China are believed to have been infected through unsafe blood-donation practices (70, 71).

CONCLUSIONS

Up to 10% of HIV-infected persons in developing countries were infected by virally contaminated blood or blood products. In developed countries, lessons learned from the AIDS crisis have led to implementation of many viral-inactivation policies and technologies that suggest a "zero tolerance" approach to maintaining blood supply safety. Fear of future litigation may be influencing policymakers in some countries. However, discussing a new technology without considering cost–benefit factors or cost-effectiveness may also be problematic. In a world of limited resources, implementing costly but not highly cost-effective procedures or policies may result in constraints in other areas and loss of previously realized benefits to a greater number of persons. There is at times a tension between societal and personal viewpoints about risks and benefits of medical procedures. This tension cannot be resolved by implementing all available new technologies when the cost is high compared with the potential benefit. Only rational policy backed by scientific evidence is likely to achieve the greatest good for the greatest number of persons in a society.

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Future Directions in the Study and Management of Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency

Moderator: Deborah P. Merke, MD; *Discussants:* Stefan R. Bornstein, MD; Nilo A. Avila, MD; and George P. Chrousos, MD

Congenital adrenal hyperplasia describes a group of inherited autosomal recessive disorders characterized by an enzymatic defect in cortisol biosynthesis, compensatory increases in corticotropin secretion, and adrenocortical hyperplasia. 21-Hydroxylase deficiency is responsible for more than 95% of cases and is one of the most common known autosomal recessive disorders. The classic or severe type presents in the newborn period or early childhood with virilization and adrenal insufficiency, with or without salt loss; the mild or nonclassic form presents in late childhood or early adulthood with mild hyperandrogenism and is an important cause of masculinization and infertility in women. This wide range of phenotypic expression is mostly explained by genetic variation, although genotype–phenotype discrepancies have been described.

Reproductive, metabolic, and other comorbid conditions, including risk for tumors, are currently under investigation in both forms of the disease. A high proportion of patients with adrenal incidentalomas may be homozygous or heterozygous for 21-hydroxylase deficiency. Women with congenital adrenal hyperplasia often develop the polycystic ovary syndrome. Ectopic adrenal rest tissue is often found in the testes of men with congenital adrenal hyperplasia; characteristic clinical and radiologic findings help differentiate this tissue from other tumors. Levels of corticotropin-releasing hormone are elevated in patients with depression and anxiety and are expected to be elevated in patients with congenital adrenal hyperplasia; it is unknown whether patients with 21-hydroxylase deficiency have an increased incidence of these psychiatric disorders. Abnormalities in both the structure and function of the adrenal medulla have been shown in patients with classic congenital adrenal hyperplasia, and the degree of adrenomedullary impairment may be a biomarker of disease severity.

The 21-hydroxylase–deficient mouse has provided a useful model with which to examine disease mechanisms and test new therapeutic interventions in classic disease, including gene therapy. Treatment of this condition is intended to reduce excessive corticotropin secretion and replace both glucocorticoids and mineralocorticoids. However, clinical management is often complicated by inadequately treated hyperandrogenism, iatrogenic hypercortisolism, or both. New treatment approaches currently under investigation include combination therapy to block androgen action and inhibit estrogen production, and bilateral adrenalectomy in the most severely affected patients. Other approaches, which are in a preclinical stage of investigation, include treatment with a corticotropin-releasing hormone antagonist and gene therapy.

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Dr. Deborah P. Merke (Warren Grant Magnuson Clinical Center, National Institutes of Health [NIH], Bethesda, Maryland): Congenital adrenal hyperplasia due to 21-hydroxylase deficiency is one of the most common known autosomal recessive disorders (1). In this condition, impaired cortisol production leads to a lack of negative glucocorticoid feedback on the pituitary, hypothalamus, and suprahypothalamic centers, resulting in an increase in corticotropin, a buildup of cortisol precursors, and androgen excess (**Figure 1**). The carrier frequency of the classic or severe form of 21-hydroxylase deficiency is approximately 1 in 60 persons (2). The carrier frequency of the nonclassic or mild form ranges from 1 in 5 to 1 in 50 persons, depending on ethnicity (3); it is most common in Hispanic and Ashkenazi Jewish populations. Because congenital adrenal hyperplasia has a high frequency, a variable presentation in children and adults, and potential complications, a thorough understanding of the disorder is of great importance to clinicians working in internal medicine, reproductive medicine, and pediatrics.

The classic form of congenital adrenal hyperplasia presents in infancy and early childhood as signs and symptoms of virilization with or without adrenal insufficiency. It is subcategorized as salt-losing or non–salt-losing, reflecting the degree of mineralocorticoid deficiency (4). In the early 1950s, cortisone therapy was found to be effective in treating adrenal insufficiency and excess androgen production in patients with congenital adrenal hyperplasia (5). Since the discovery of cortisone therapy and the addition of mineralocorticoid supplementation, the morbidity and mortality of pa-

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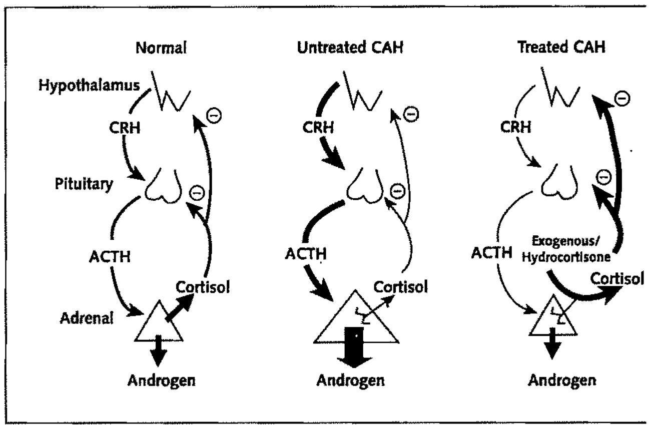
tients with classic disease have markedly decreased, and these patients now have a long life span. Thus, long-term consequences of current treatments are an important consideration.

The 21-hydroxylase–deficient mouse, which was described in a Japanese study by Shiroishi and coworkers (6), has been a useful model for gaining new insights into the pathophysiology of the disease in humans and for developing new therapeutic strategies. The mouse model revealed an abnormal hypothalamic–pituitary–adrenal feedback mechanism (7), alterations in the structure and function of the adrenal medulla (8), and a good response to gene therapy (9). Further exploration of the disease process in this animal model is an essential aspect of the bench-to-bedside research approach to improving the human condition.

Abnormalities in both the structure and function of the adrenal medulla have been shown in patients with classic congenital adrenal hyperplasia (10). This finding may explain why some children with the severe form of 21-hydroxylase deficiency are prone to adrenal crises, hypoglycemia, and cardiovascular collapse in response to febrile illnesses or other stressful circumstances, despite adequate glucocorticoid replacement.

There are many unresolved clinical problems in the management of classic 21-hydroxylase deficiency in both males and females. Among the most critical are inadequate response to glucocorticoid and mineralocorticoid replacement therapy, iatrogenic Cushing syndrome (11), adult short stature (12, 13), and oligo-amenorrhea and infertility in women (14, 15). The new treatment approaches to classic congenital adrenal hyperplasia represent potential solutions to these unresolved issues. In a long-term randomized clinical trial, the NIH is testing a new treatment regimen consisting of reduced hydrocortisone dose, an antiandrogen, and an aromatase inhibitor (16, 17). Bilateral adrenalectomy is being performed in selected cases (18). Future therapies include a new class of drug called corticotropin-releasing hormone antagonists (19) and possibly gene therapy (9).

Figure 1. **Congenital adrenal hyperplasia (*CAH*) due to 21-hydroxylase deficiency.**



In a person with normal adrenal function (*left*), the adrenal gland produces both cortisol and androgen. The hypothalamic-pituitary-adrenal axis is controlled by negative feedback. In the untreated patient with CAH (*middle*), a block in cortisol biosynthesis leads to a buildup of cortisol precursors and lack of negative feedback. Corticotropin (*ACTH*) is oversecreted, and adrenal hyperplasia occurs. The combination of accumulated cortisol precursors and increased ACTH results in massive androgen production. In the treated patient with CAH (*right*), exogenous hydrocortisone replacement reduces androgen production. Supraphysiologic doses of hydrocortisone are often necessary to adequately suppress androgen production. CRH = corticotropin-releasing hormone.

Nonclassic congenital adrenal hyperplasia, the mild form of the disease, is a common cause of hyperandrogenism in women. Although the same gene is involved in both the severe and mild forms, genetic mutations typically associated with the mild form of the disease only partially impair 21-hydroxylase activity. Thus, the patient with nonclassic congenital adrenal hyperplasia is in a fully compensated state; she does not have cortisol deficiency but rather manifestations of hyperandrogenism, usually later in childhood, around puberty, or in early adulthood (20, 21). Nonclassic congenital adrenal hyperplasia is an important consideration in the differential diagnosis of female patients with symptoms or signs of hyperandrogenism, such as severe cystic acne, hirsutism, male pattern baldness, oligo-amenorrhea, or infertility. Nonclassic 21-hydroxylase deficiency, especially when it exists in conjunction with hyperinsulinemia, often results in the polycystic ovary syndrome, with its characteristic reproductive and metabolic comorbid conditions. Recognition of this disorder is crucial for family planning and management in women with hyperandrogenism. Men with nonclassic congenital adrenal hyperplasia are usually asymptomatic but may also present with early puberty or testicular adrenal rests.

Another recognized comorbid condition associated with congenital adrenal hyperplasia is activation of ectopic adrenal tissue resulting in adrenal rest tumors (22). These tumors are most commonly found in the testes of men with classic or nonclassic congenital adrenal hyperplasia and often result in oligo-azoospermia and infertility (23). New advances in the diagnostic evaluation and management of these tumors are presented in this paper.

GENETICS

The gene for 21-hydroxylase lies on chromosome 6 within the HLA locus of the major histocompatibility system; thus, 21-hydroxylase deficiency is an HLA-linked disorder (24). Two homologous genes result from ancestral duplication. *CYP21B* is the active gene; *CYP21A* is an inactive pseudogene.

The location of the *CYP21B* gene makes it vulnerable to relatively large genomic DNA exchanges with its homologous gene, *CYP21A*. The proximity of these genes and their location within the HLA region, which has a high rate of recombination, facilitate such exchanges. Therefore, the 21-hydroxylase locus shows an unusual degree of variability between individuals (25, 26). 21-Hydroxylase deficiency is unique because most mutations result from the transfer of sequences between pseudogenes and active genes (27). When deleterious sequences that normally present in the pseudogene are transferred to the active gene, they render the gene incapable of encoding a normal enzyme. The term *gene conversion* is used to denote the transfer of sequences between homologous genes; however, the mechanism is poorly understood.

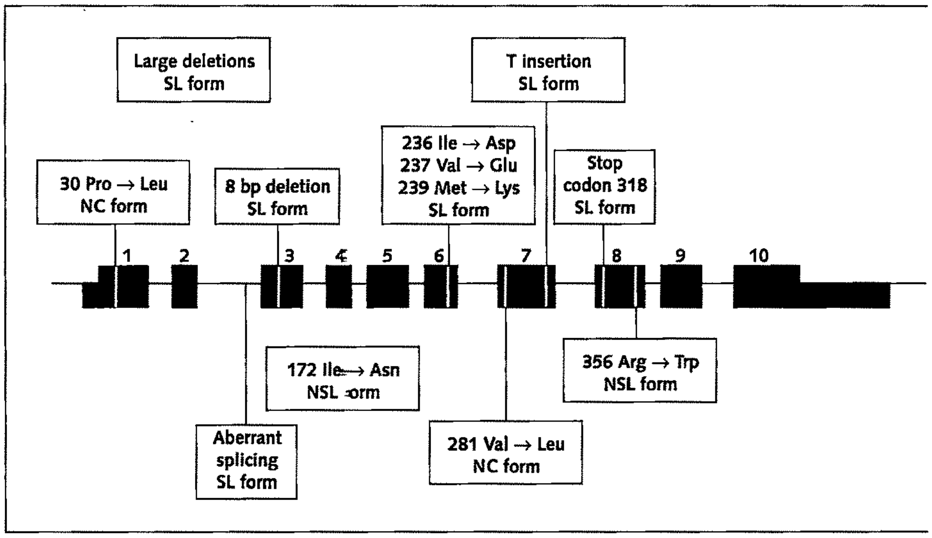
Specific mutations typically correspond to the three types of 21-hydroxylase deficiency: salt-losing, non–salt-losing (simple virilizing), and nonclassic congenital adrenal hyperplasia (**Figure** 2). In vitro studies have shown that mutations resulting in complete inactivation of 21-hydroxylase activity are associated with the salt-losing phenotype, those that reduce 21-hydroxylase activity to approximately 2% are associated with the non–salt-losing phenotype, and those that reduce 21-hydroxylase activity to 10% to 75% are associated with the nonclassic phenotype (28, 29) (**Figure** 2). Most patients are compound heterozygotes, and the severity of the disease is determined by the activity of the less severely affected allele.

The degree of functional impairment predicted by individual mutations usually corresponds to the clinical severity observed in a given patient. However, genotype does not always accurately predict phenotype. This disparity between genotype and phenotype may be due to androgen sensitivity or to other genes that cause differences in steroid metabolism and homeostasis.

ANIMAL MODEL FOR 21-HYDROXYLASE DEFICIENCY

Dr. Stefan R. Bornstein (Pediatric and Reproductive Endocrinology Branch, National Institute of Child Health and Human Development [NICHD], NIH): In

Figure 2. **The 10 most common genetic mutations found in 21-hydroxylase deficiency.**



The location and nature of each microconversion and the expected clinical phenotype (salt-losing [*SL*], non–salt-losing [*NSL*], and nonclassic congenital adrenal hyperplasia [*NC*]) are shown. The 10 exons and 9 introns of *CYP21B* are drawn to scale. Arg = arginine; Asn = asparagine; Asp = aspartate; Glu = glutamate; Ile = isoleucine; Leu = leucine; Lys = lysine; Met = methionine; Pro = proline; Trp = tryptophan; Val = valine.

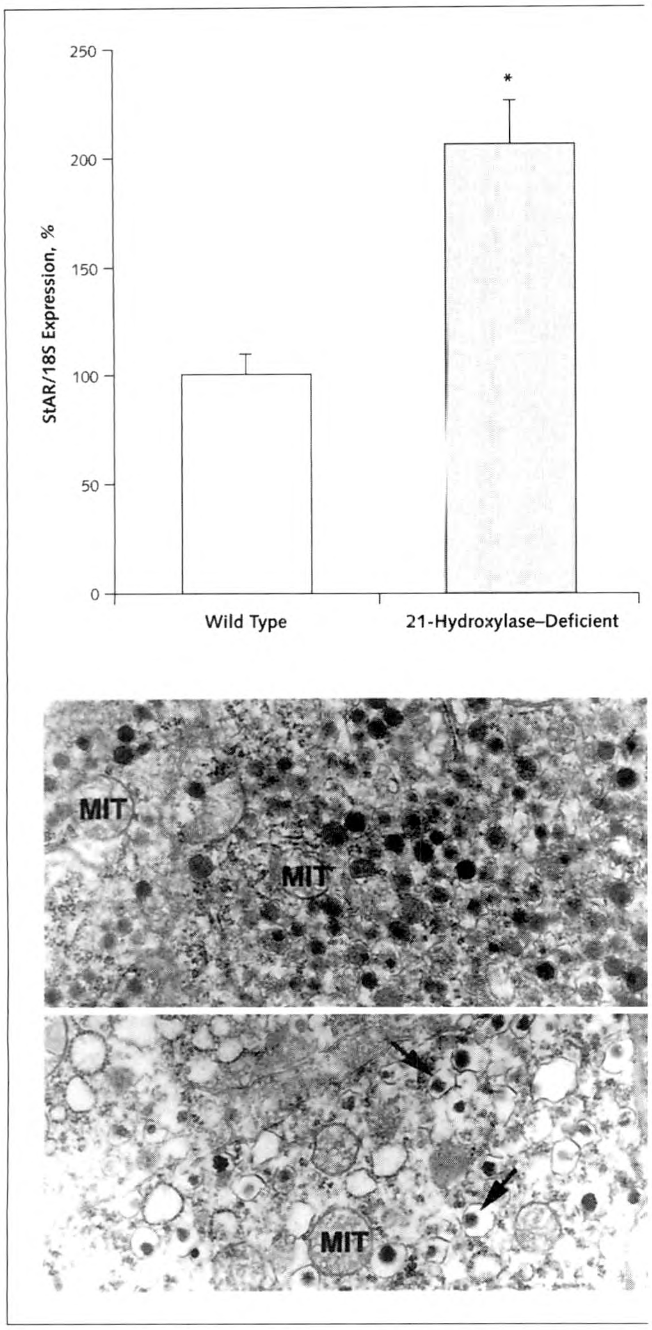
the mouse, the 21-hydroxylase gene also lies within the major histocompatibility locus (30). Mice with spontaneous 21-hydroxylase deficiency have a deletion of the 21-hydroxylase gene (6, 7, 31). 21-Hydroxylase activity is completely absent in newborn mice homozygous for this deletion, and this absence is lethal in the early postnatal stage.

The deficiency of glucocorticoids results in adrenocortical hyperplasia and plasma accumulation of precursor steroids in both mice and humans with congenital adrenal hyperplasia. In mice, which normally lack adrenal 17-α-hydroxylase, the enzymatic blockade results mainly in accumulation of progesterone. Most of the affected mice, if not treated with glucocorticoids and mineralocorticoids, die within 1 week (6, 7, 31). Although the disease state of the 21-hydroxylase–deficient mouse is not completely comparable to human congenital adrenal hyperplasia, it has provided a useful model with which to examine molecular and cellular mechanisms of the disease and test new therapeutic interventions.

The adrenal glands of affected mice demonstrate a significant increase in expression of messenger RNA of steroidogenic acute regulatory protein (**Figure 3**), which is the rate-limiting step for steroidogenesis (32). Corticotropin regulates the expression of this protein, and the increase of messenger RNA reflects impaired negative feedback with increased corticotropin production. Moreover, one study showed that prenatal dexamethasone treatment (0.5 to 2 μg/d) failed to adequately suppress fetal adrenal hormones in mice, suggesting hyperactivity of the hypothalamic–pituitary corticotroph axis and insensitivity to glucocorticoid feedback inhibition (7). Intrauterine glucocorticoid deficiency may affect the sensitivity of feedback inhibition postnatally, thus blunting the central effects of treatment.

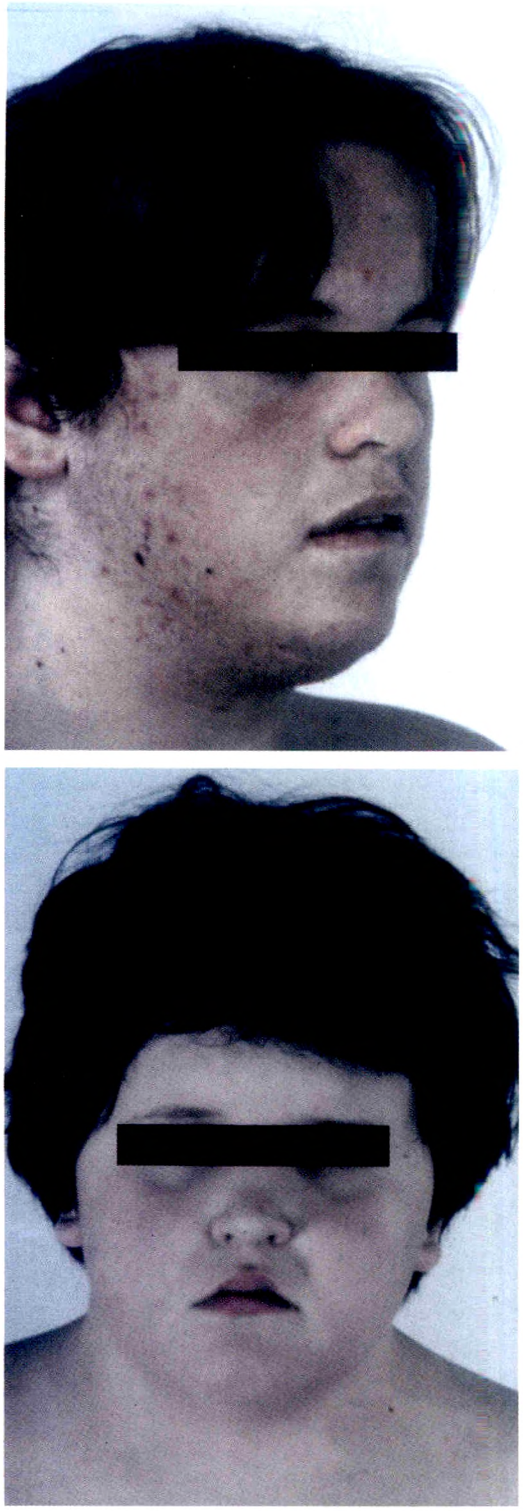
The animal model allowed a detailed analysis of morphologic changes of the adrenal glands in the setting of 21-hydroxylase deficiency (7, 8, 31). The adrenal cortex of mutant mice was markedly enlarged with adrenocortical cell hyperplasia and incomplete migration of chromaffin cells in the center of the gland. In addition,

Figure 3. **The 21-hydroxylase–deficient mouse.**



Top. Steroidogenic acute regulatory protein (*StAR*) expression is increased in the adrenal glands of mice with 21-hydroxylase deficiency, as compared with wild-type animals. Quantitative steroidogenic acute regulatory protein was determined by TaqMan PCR Core Reagents Kit (Applied Biosystems, Foster City, California) ($n = 4$ adrenal glands; $P < 0.05$). Amounts of RNA were calculated with relative standard curves for both steroidogenic acute regulatory protein and 18S. The amount of messenger RNA was corrected by division by the amount of 18S RNA in each sample. **Middle.** Electromicrograph showing catecholamine-storing secretory vesicles in chromaffin cells of control animals (size range, 50 to 450 nm). **Bottom.** Electromicrograph of chromaffin cells. Secretory granules are markedly reduced in chromaffin cells of 21-hydroxylase–deficient mice. The remaining granules are predominantly electron-dense, norepinephrine-containing vesicles, lying in large lucent vacuoles (*arrows*). For parts B and C, stain is uranyl acetate and lead citrate, and magnification is × 15 000. MIT = mitochondria.

Figure 4. **Patients with salt-losing 21-hydroxylase deficiency.**



The treatment outcome in classic congenital adrenal hyperplasia is often suboptimal because of incomplete suppression of hyperandrogenism (*top*), treatment-induced hypercortisolism (*bottom*), or both. At 16 years of age, a female patient with salt-losing 21-hydroxylase deficiency due to undertreatment with glucocorticoid and elevated androgen levels had hirsutism, acne, amenorrhea, and hyperpigmentation (*top*). Increased glucocorticoid treatment resulted in weight gain with cushingoid features and short stature in a male patient with classic 21-hydroxylase deficiency (*bottom*).

secretory vesicles were depleted and adrenal catecholamine levels were reduced in chromaffin cells (**Figure 3**, *middle*) (8). Apparently, the sympathoadrenomedullary system, as well as the adrenal cortex, is affected in the 21-hydroxylase–deficient mouse.

In chromaffin cells, expression of phenylethanolamine-*N*-methyltransferase, the enzyme that converts norepinephrine to epinephrine, is stimulated by glucocorticoids (33–37). In concordance with this, epinephrine deficiency was reported in children with hypocorticotropic hypopituitarism (38). Therefore, the absence of normal secretion of adrenocortical corticosterone is probably responsible for the impaired production of adrenal catecholamines in mice with 21-hydroxylase deficiency. However, exogenous replacement of glucocorticoid did not restore chromaffin cell function in 7-day-old mice. This supports the finding of reduced epinephrine levels in patients with Addison disease who are given adequate hydrocortisone replacement (39).

On the basis of these findings in mice with 21-hydroxylase deficiency, we investigated adrenomedullary function in humans with congenital adrenal hyperplasia and found a similarly severe impairment of both the structure and function of the adrenal medulla (10). This finding may have important clinical implications for the cardiovascular fragility that is often characteristic of such patients.

Mice with 21-hydroxylase deficiency have also proven useful in testing novel therapeutic strategies. In a model for genetic treatment of the disease in humans, a recombinant DNA fragment containing the murine genomic gene for 21-hydroxylase was successfully introduced into the adrenal glands of mutant mice (40). Although only 15% of newborns were typically rescued by synthetic steroid therapy, the efficiency of rescue was increased to 80% with the use of gene therapy (40).

We recently replaced the defective enzyme in the adrenal glands of the mouse model using an adenoviral vector encoding the genomic sequence of the human

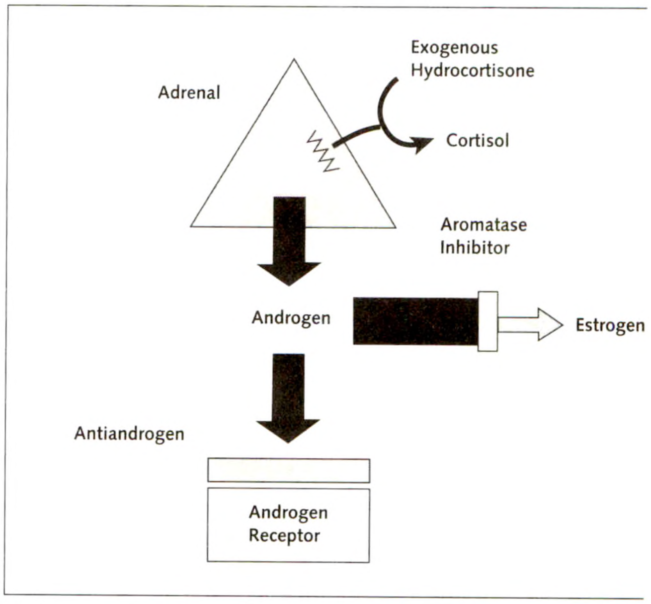
CYP21 gene (*AdCYP21*) (9). In homozygous 21-hydroxylase–deficient mice, intra-adrenal injections of *AdCYP21* allowed expression of human *CYP21* messenger RNA and 21-hydroxylase activity in the adrenal gland, as well as restored adrenal zonae, mitochondrial ultrastructure, and plasma corticosterone levels (9). Furthermore, adrenal gene transfer of the *CYP21* gene also corrected the abnormalities of the adrenal medulla; catecholamine secretory granules were restored (unpublished observation). The adenoviral vectors induced almost no inflammatory response in the adrenal glands, suggesting that high local glucocorticoid concentration suppresses the immune response caused by these vectors in other tissues. The adrenal gland may therefore be an ideal site for gene therapy, an observation that has been made elsewhere (41).

The adrenal cortex and medulla have a close functional relationship (42–47). Animal models with defined defects in the adrenal gland provide valuable and novel insights into the development, cross-talk, and functioning of the stress system and allow the testing of new therapeutic strategies (48). Unlike in exogenous hormone replacement therapy, adrenal gene transfer corrects the gene defect in 21-hydroxylase deficiency and thereby corrects abnormalities in both endocrine limbs of the stress system (9). Development of novel viral vectors (most likely retroviral vectors that allow stable long-term integration) with adrenal-specific promoters will be required to improve the efficiency and duration of gene transfer in the adrenal gland. With these advances, gene therapy may become a feasible option for treatment of congenital adrenal hyperplasia.

CLASSIC 21-HYDROXYLASE DEFICIENCY

Dr. Deborah P. Merke: Defects in the 21-hydroxylase gene, which significantly impair or even eliminate 21-hydroxylase activity, result in classic congenital adrenal hyperplasia, the most severe form of the disease. Females with classic congenital adrenal hyperplasia typically present at birth with ambiguous genitalia because of exposure to high levels of androgens in utero. Occasionally, genital ambiguity can be profound enough to cause incorrect sex assignment at birth. The age at diagnosis in males varies according to the severity of mineralocorticoid deficiency or salt loss. Males with salt loss typically present at 7 to 14 days of life with vomiting, weight loss, lethargy, hyponatremia, and hyperkalemia. Males without salt loss present with precocious puberty, characterized by pubic hair and accelerated growth at 2 to 4 years of age (4).

Figure 5. **An investigational approach to the treatment of classic congenital adrenal hyperplasia.**



Fludrocortisone is given in the usual manner. The hydrocortisone dose is reduced to physiologic levels, resulting in elevated androgen production. An antiandrogen agent is administered to block the effect of the elevated androgen levels, and an inhibitor of androgen-to-estrogen conversion is given to block conversion of the increased amount of androgen to estrogen.

A markedly elevated 17-hydroxyprogesterone level ($>$242.4 nmol/L [normal value $<$ 8.9 nmol/L]) is a diagnostic indicator of classic 21-hydroxylase deficiency (28). A corticotropin stimulation test is unnecessary because random, unstimulated levels are markedly elevated. Typically, patients with salt loss have higher 17-hydroxyprogesterone levels than those without salt loss. Genetic analysis is also available and is often used for prenatal testing by chorionic villous sampling (49).

Treatment of classic congenital adrenal hyperplasia is intended to reduce excessive corticotropin secretion and replace both glucocorticoid and mineralocorticoid hormones. Glucocorticoid replacement in children is usually accomplished with oral hydrocortisone. In some patients with classic 21-hydroxylase deficiency, satisfactory control of androgens can be achieved with 12 to 15 mg/m^2 of hydrocortisone per day; however, higher doses are often needed to adequately reduce androgen production (50). Because of the well-known risks of excessive glucocorticoid use, we are reluctant to exceed 25 mg/m^2 per day. Longer-acting glucocorticoids, such as prednisone (5 to 7.5 mg/d, divided into two doses) and dexamethasone (0.25 to 0.4 mg at bedtime), may be used in adults but are avoided in children because they may suppress growth.

Mineralocorticoid replacement is accomplished with fludrocortisone. We encourage patients to use salt freely to satisfy salt cravings and adjust mineralocorticoid dose to maintain a normal plasma renin activity for the level of salt intake. A typical oral dose of fludrocortisone ranges from 100 to 200 μg/d; rarely, a patient may require a higher dose. The dose of fludrocortisone is relatively independent of body size from childhood to adulthood. Insufficient replacement with fludrocortisone results in hypovolemic stimulus of corticotropin. Many patients with non–salt-losing disease have elevated plasma renin activity. Therefore, fludrocortisone therapy in such patients allows management with lower doses of glucocorticoid (50).

At physiologic doses, hydrocortisone prevents adrenal insufficiency but does not suppress corticotropin and androgen production. Higher doses of hydrocortisone are necessary to adequately suppress androgens (50). Clinical management of classic congenital adrenal hyperplasia is often a difficult balancing act between two undesirable states: hyperandrogenism and hypercortisolism (**Figure** 4). The signs of hypercortisolism are characteristic of iatrogenic Cushing syndrome: obesity, short stature, osteoporosis, carbohydrate intolerance, and dyslipidemia. The symptoms and signs of hyperandrogenism include virilization of females, precocious virilization of males, early puberty, and adult short stature in both sexes.

New Treatment Approaches

Androgen Antagonism

Androgen antagonist approaches are designed to optimize hormonal control and adult outcome in patients with classic congenital adrenal hyperplasia. These goals entail controlling the effect of excess adrenal androgen and reducing glucocorticoid dose. At the NIH, a long-term randomized study is evaluating a new treatment approach (17). Instead of using high-dose hydrocortisone to suppress androgens, we use lower doses of hydrocortisone and allow levels of corticotropin and androgens to remain mildly elevated. We then antagonize the effects of androgens with an androgen-receptor antagonist (flutamide) and block the conversion of androgen to estrogen with testolactone, an aromatase inhibitor (**Figure** 5). Blocking estrogen production is important because estrogens advance bone age and induce early puberty.

In this NIH study, half of the participating children received reduced doses of hydrocortisone and appropriate doses of fludrocortisone, as well as flutamide and testolactone; the other half received conventional doses of hydrocortisone and fludrocortisone. On average, children in the investigational group received half the dosage of hydrocortisone compared with the children in the control group (mean dosage [±SD], 8.6 ± 0.6 vs. 13.3 ± 0.6 mg/m^2 per day) (17). As expected, after 2 years of therapy, we found significantly higher levels of 17-hydroxyprogesterone, androstenedione, and testosterone in the investigational group than in the control group (17). Despite these elevated hormone levels, however, children receiving the new treatment regimen had normalized growth velocity and bone maturation. Thus, this new regimen represents a promising new treatment approach for children with classic 21-hydroxylase deficiency.

Bilateral Adrenalectomy

Bilateral adrenalectomy has been proposed recently as a surgical treatment option for severe classic congenital adrenal hyperplasia (18, 51). To date, five such operations have been reported (52–56); all were done in difficult-to-control cases, and one was performed laparoscopically (51, 54). The argument for adrenalectomy is that concern about progressive virilization is eliminated once the adrenal glands are removed. Arguments against the procedure include risks of surgery and anesthesia; its irreversibility, which eliminates the option of new medical approaches; activation of adrenal rest or ectopic adrenal tissue; and theoretical loss of possibly protective adrenomedullary function. As we observed in the mouse model, the adrenal medulla does not function normally in patients with this disorder (10). There are two approaches to adrenalectomy: 1) Perform a bilateral adrenalectomy in severely affected patients with difficult-to-control disease, or 2) perform an adrenalectomy in the first year of life, concurrent with genitoplasty in females (18). However, predicting disease severity in the first year of life is difficult, and genotyping is not sufficient because of genotype–phenotype variation (27, 28).

Adrenomedullary Function in Congenital Adrenal Hyperplasia

Evaluation of the adrenal medulla may be useful in predicting disease severity. We evaluated adrenal morphologic characteristics and adrenal function in patients with 21-hydroxylase deficiency (10). Similar to the mouse model, our study found incomplete formation of the adrenal medulla in three patients with 21-hydroxylase deficiency who had bilateral adrenalectomy. Of interest, we also found that patients with 21-hydroxylase deficiency who had very low, even undetectable levels of 24-hour urinary epinephrine were categorized as salt-losing and were hospitalized for adrenal crises.

The use of an antiandrogen in combination with an aromatase inhibitor and a reduced hydrocortisone dose is a promising new treatment approach to optimize growth, development, and adult height in patients with classic congenital adrenal hyperplasia. Adrenalectomy should be considered in selected cases. Adrenomedullary function is impaired in patients with 21-hydroxylase deficiency and may be a biomarker for disease severity.

NONCLASSIC CONGENITAL ADRENAL HYPERPLASIA

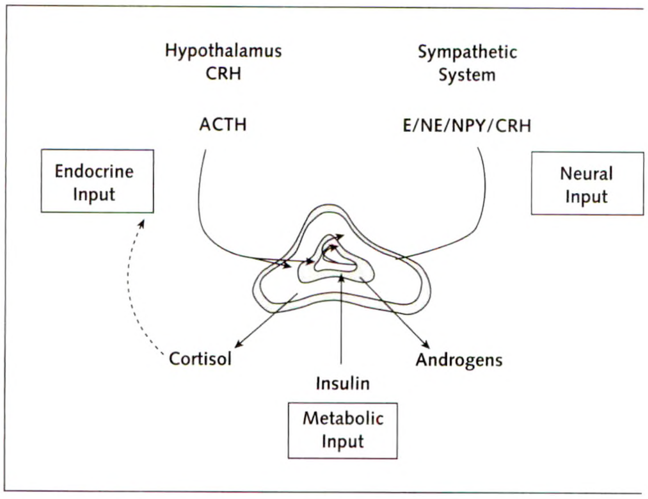
Dr. George P. Chrousos (Pediatric and Reproductive Endocrinology Branch, NICHD, NIH): The nonclassic form of 21-hydroxylase deficiency is mild and is most often recognized in late puberty and early adulthood. One of the first families diagnosed with nonclassic congenital adrenal hyperplasia was studied at the NIH in the early 1980s (57). Until that time, the existence of this condition was in doubt, yet it is quite common in some populations and has characteristic reproductive, metabolic, and other comorbid conditions. Our first patient with nonclassic congenital adrenal hyperplasia was 1 of 2 from a sample of 40 women consecutively admitted to the NIH with hirsutism (57). All of the patients had serial 24-hour sampling for measurement of plasma 17-hydroxyprogesterone concentrations and a corticotropin stimulation test. In the 24-hour sampling, 17-hydroxyprogesterone was secreted in both a circadian and pulsatile fashion with elevations in the early morning and most values within the normal range. These findings were later confirmed in a larger study, which found elevated levels of adrenal androgens occurring primarily during the early morning hours (21, 58).

Results of a random test of plasma 17-hydroxyprogesterone level may be normal in a patient with nonclassic congenital adrenal hyperplasia. A 30- or 60-minute corticotropin test with a 17-hydroxyprogesterone level greater than 45.5 nmol/L is usually necessary to diagnose this disorder, although cutoff levels reported for the diagnosis of nonclassic congenital adrenal hyperplasia vary from 30.3 nmol/L (59) to 60.6 nmol/L (60). Early-morning basal 17-hydroxyprogesterone level can be used for screening (61), but it is not as sensitive or specific as a corticotropin test. Heterozygote carriers of congenital adrenal hyperplasia often have mildly elevated 17-hydroxyprogesterone levels (<30.3 nmol/L) in a corticotropin stimulation test (28), but they do not have symptoms or signs of the disease. In the rare case of a patient whose corticotropin-stimulated 17-hydroxyprogesterone level is between 30.3 nmol/L and 45.5 nmol/L, genetic analysis may be necessary to distinguish a heterozygote carrier from a homozygously affected patient with a mildly deleterious mutation in the 21-hydroxylase gene.

A glucocorticoid, a birth control pill, an antiandrogen, or combinations of these medications are used to treat women with nonclassic congenital adrenal hyperplasia. Spironolactone and flutamide, which are not formally approved for this indication, are the typical antiandrogens used. Birth control pills protect the ovaries from becoming polycystic, sclerotic, and androgen-secreting and prevent the birth of undermasculinized male children in women taking antiandrogens. In studies of female transsexuals, up to 70% developed the polycystic ovary syndrome secondary to exogenous hyperandrogenism (62). Thus, it is extremely important to diagnose nonclassic congenital adrenal hyperplasia and start therapy as early as possible. Early treatment prevents the vicious cycle of progressive deterioration and sclerosis of the ovaries, a process that is accelerated and worsened by the concurrent presence of insulin resistance (63). When fertility is desired, glucocorticoid therapy (usually prednisone) is often necessary and combination therapy with the antiandrogen and birth control pill is discontinued.

Men with nonclassic congenital adrenal hyperplasia typically do not require treatment. Occasionally, how-

Figure 6. **Mechanisms of adrenal hyperandrogenism.**



Elevations in adrenocorticotropic hormone, increases in neural–adrenomedullary input, and presence of insulin-mediated metabolic input may lead to adrenal hyperandrogenism and premature adrenarche. In turn, adrenal hyperandrogenism, insulin resistance, or both may lead to full-blown polycystic ovary syndrome in a woman with an inherent ovarian vulnerability. ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; E = epinephrine; NE = norepinephrine; NPY = neuropeptide Y.

ever, males with nonclassic congenital adrenal hyperplasia present with slightly advanced puberty and bone age. These boys may be at risk for early epiphyseal fusion and adult short stature and might benefit from glucocorticoid therapy during childhood. Rarely, glucocorticoid treatment is indicated in adult men to suppress the development of testicular adrenal rest tissue.

REPRODUCTIVE, METABOLIC, AND OTHER COMORBID CONDITIONS ASSOCIATED WITH CONGENITAL ADRENAL HYPERPLASIA

Reproductive Comorbid Conditions

Females with classic congenital adrenal hyperplasia are born with varying degrees of genital virilization. Exposure to androgens in early fetal life causes labial fusion and the formation of a urogenital sinus, pigmentation and rugation of the labia, and clitoromegaly. Occasionally, genital ambiguity can be severe enough to cause the wrong sex assignment at birth. This severe virilization can now be repaired surgically with a single procedure in the first few months of life (64). However, other surgical approaches often involve several procedures during childhood and early adulthood. Scarring may cause vaginal stenosis, which requires dilatation before a patient is able to have intercourse. Affected women therefore often face physical and psychological barriers to sexual function (65).

Despite these complex psychosexual and biological issues, many women with classic congenital adrenal hyperplasia, particularly the non–salt-losing form, marry and have children. However, women with congenital adrenal hyperplasia may have decreased fertility if their adrenal androgens are not suppressed adequately. The polycystic ovary syndrome may develop secondary to adrenal hyperandrogenism. The effect of ovarian exposure to adrenal androgens prenatally and during childhood is unknown, but it may predispose these women to the polycystic ovary syndrome.

In children and women with nonclassic congenital adrenal hyperplasia, hyperandrogenism is the key morbidity factor. Nonclassic congenital adrenal hyperplasia accounts for about 5% to 10% of children with premature adrenarche and 5% to 10% of women with hirsutism (57, 66–68). The clinical spectrum includes early adrenarche in both girls and boys, menstrual irregularities (mostly oligo-menorrhea), adolescent and postadolescent cystic acne, hirsutism, male pattern baldness, polycystic ovaries, oligo-anovulation, and infertility. In theory, women with nonclassic disease should have increased risk for cancer of the reproductive system as a result of anovulation and unopposed estrogen action, but this has not been shown.

In men, growth of adrenal rest tissue in the testes may lead to testicular tenderness and pain, oligospermia or azoospermia, and infertility. Rarely, men with nonclassic congenital adrenal hyperplasia present with a markedly enlarged and tender testis and oligospermia due to testicular adrenal rests (69). Oligospermia is caused by destruction of the tubuli efferentes, which bring incapacitated spermatozoa from the spermatic tubules to the epididymis. With the advances in fertility technologies, affected patients can father children by using sperm obtained directly from the testis to fertilize the mother's ova in vitro.

Metabolic Comorbid Conditions

Patients with congenital adrenal hyperplasia who are exposed to excessive doses of glucocorticoids may develop iatrogenic Cushing syndrome and all its metabolic comorbid conditions. Nonclassic congenital adrenal hyperplasia affects approximately 0.5% of the female population. Patients with simultaneous mild enzymatic deficiency of 21-hydroxylase and insulin resistance may develop premature adrenarche or the full-blown polycystic ovary syndrome (**Figure 6**). Insulin resistance may be genetic, constitutional, or both and may be further aggravated by obesity. The polycystic ovary syndrome affects approximately 5% to 7% of women of reproductive age (63), and at least one quarter of patients with nonclassic congenital adrenal hyperplasia have full-blown polycystic ovary syndrome associated with the metabolic syndrome X and its long-term sequelae, atherosclerosis and cardiovascular disease (**Figure 7**). Our first patient with nonclassic congenital adrenal hyperplasia had already developed full-blown polycystic ovary syndrome at the time of her diagnosis because she was also insulin resistant (57). To conceive her two children, she required treatment with dexamethasone and clomiphene.

Adrenal Tumors

Congenital adrenal hyperplasia may be associated with increased incidence of adrenal adenomas or incidentalomas. On magnetic resonance imaging of the adrenal glands, patients with both classic and nonclassic congenital adrenal hyperplasia frequently have nonsecretory adrenocortical adenomas (70). One of 10 patients with congenital adrenal hyperplasia had an adenoma greater than 5 cm in diameter, which indicates surgical removal (43, 71). Of interest, carriers of classic and nonclassic congenital adrenal hyperplasia, who are not expected to have any endocrine or other abnormalities, also develop such tumors in their adrenal glands. One in 20 of these patients has tumors that exceed 5 cm in diameter (70). Rough calculations indicate that a significant proportion of all patients with incidentalomas have nonclassic congenital adrenal hyperplasia or are carriers for congenital adrenal hyperplasia (43, 71).

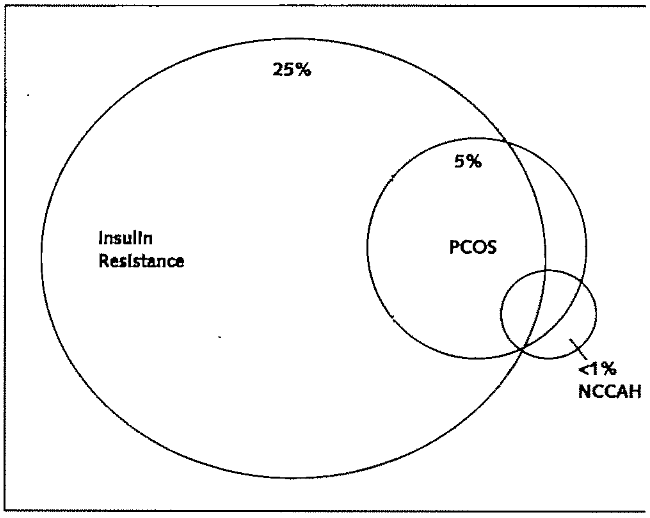
EVALUATION AND MANAGEMENT OF ADRENAL REST TISSUE

Diagnosis and Radiologic Evaluation

Dr. Nilo A. Avila (Diagnostic Radiology Department, Warren Grant Magnuson Clinical Center, NIH): Ectopic adrenal rest tissue is biochemically identical to that of the adrenal cortex (72–74) and can function like adrenal tissue; its function is increased by corticotropin and decreased by high doses of glucocorticoids. Persistent virilization in selected patients with congenital adrenal hyperplasia has been attributed to activated adrenal rest tissue (75). Embryologically, both the gonads and the adrenal glands originate from the mesoderm of the urogenital ridge; therefore, adrenal rest tissue is most frequently found in the gonads, although it may occur in other parts of the body. It is most often found in the testes, where it is called testicular adrenal rest tissue (22). It has also been described in the celiac plexus, broad ligaments, and ovaries (76–79). Characteristic radiologic features of testicular adrenal rest tissue have been described (22, 80, 81). The rare diagnosis of ovarian adrenal rest has been based on biopsy and pathologic examination, with such nonspecific radiologic findings as ovarian enlargement (79).

At the NIH, we performed testicular ultrasonography on 42 patients with classic congenital adrenal hyperplasia and found that approximately 30% had testicular masses (81). Only two of the patients with positive findings (5%) had palpable masses. Thus, physical examination misses most of the masses found on testicular ultrasonography. The clinical significance of small (<5 mm) testicular adrenal rest tissue, which is detected only by screening ultrasonography, is unknown.

Figure 7. **Venn diagram including the overlapping populations of women with insulin resistance, the polycystic ovary syndrome (*PCOS*), and nonclassic congenital adrenal hyperplasia (*NCCAH*).**



Several ultrasonographic features are characteristic but not pathognomonic of testicular adrenal rest tissue (**Figure 8A** and **8B**). The bilateral nature of these masses is important because other testicular tumors, including testicular cancer, tend to be unilateral. If blood flow is present, color Doppler will demonstrate undisturbed blood flow through testicular adrenal rest tissue, whereas solid testicular carcinoma tends to divert vascular structures (22).

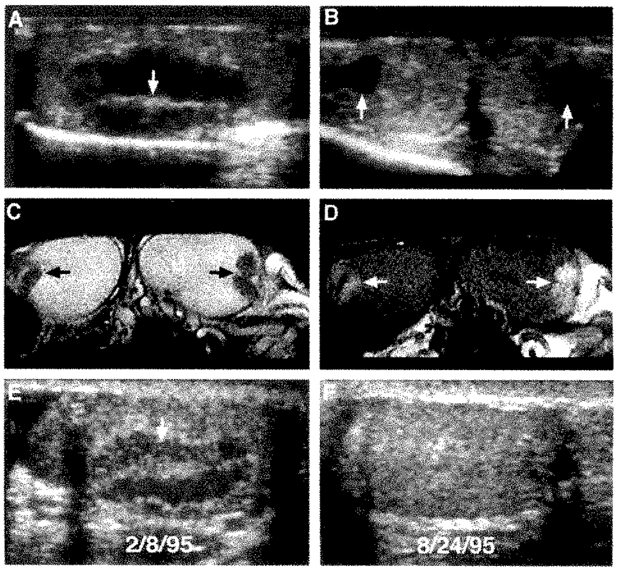
The features of testicular adrenal rest tissue on magnetic resonance imaging are similar to those of normal adrenal glands (80). Most of these masses are isointense on T1-weighted images, hypointense on T2-weighted images (**Figure 8C**), and are diffusely enhanced on post-contrast images (**Figure 8D**). Because ultrasonography is more available and less expensive than magnetic resonance imaging, it should be the method of choice in the diagnosis and follow-up of testicular adrenal rest tissue.

Treatment and Follow-up

It is important to recognize adrenal rest tissue as a cause of intratesticular masses in men with congenital adrenal hyperplasia because glucocorticoid therapy, rather than surgery, is the appropriate treatment. Higher-dose glucocorticoid therapy may be warranted if the patient is symptomatic or infertile, while standard treatment is indicated for small testicular adrenal rest tissue. The clinician should balance the need for shrinkage of testicular adrenal rest tissue with the iatrogenic side effects of increased glucocorticoid therapy, especially because the significance of small testicular adrenal rest tissue is unknown. If the mass rapidly increases in size or is unresponsive to glucocorticoid therapy, further evaluation, such as testicular venous sampling or a testicular biopsy, may be performed to confirm the diagnosis (82, 83). Orchiectomy is the treatment of choice for testicular neoplasms but is rarely indicated for testicular adrenal rest tissue (72, 84, 85). Suspicion of carcinoma or unrelieved pain and tenderness are the major indications for an orchiectomy. If orchiectomy is performed, a testicular prosthesis is recommended.

Although the cause of testicular adrenal rest tissue is unknown, large symptomatic masses tend to occur in patients with very high levels of corticotropin and typically respond to glucocorticoid therapy (**Figure 8E** and **8F**). In the past, many physicians did not treat men with classic congenital adrenal hyperplasia in adulthood unless treatment was required for extreme salt loss. There is now enough evidence of risk for testicular adrenal rest tissue and infertility (23, 73, 86) to warrant lifetime glucocorticoid therapy in men with classic congenital adrenal hyperplasia.

Figure 8. **Characteristic radiologic features of testicular adrenal rest tumors.**



Testicular adrenal rest tissue masses often surround the mediastinum testes (*arrow*) (*A*), and are bilateral, intratesticular, and hypoechoic (*B*). Testicular adrenal rest tissue masses are seen equally as well on ultrasonography and magnetic resonance imaging. Most of these masses are hypointense on T2-weighted images (*C*) and isointense on T1-weighted images, with diffuse enhancement post-contrast (*D*). Large testicular adrenal rest tissue (*E*) typically shrinks or disappears (*F*) with higher-dose glucocorticoid therapy.

CONCLUSIONS AND FUTURE DIRECTIONS

Dr. George P. Chrousos: Congenital adrenal hyperplasia is a disease of widely varying severity. In the classic form, the therapeutic spectrum of cortisol is very narrow and the addition of antiandrogens may help with optimizing control (11). The addition of an aromatase inhibitor may be a necessary adjunct to moderate the conversion into estrogens of androgens diverted from the androgen receptor (17). Bilateral adrenalectomy may be necessary in some patients who cannot be controlled medically (18, 52). Adrenal rest tumors are often present in the testes of males with classic or nonclassic congenital adrenal hyperplasia. Characteristic radiologic features help differentiate these tumors from testicular carcinoma. Undiagnosed nonclassic congenital adrenal hyperplasia should be considered in patients with testicular tumors (69), and nonclassic congenital adrenal hyperplasia, the congenital adrenal hyperplasia carrier state, or both should be considered in patients with adrenal incidentalomas (70).

Several important questions will have to be answered in the next few years. Increased secretion of hypothalamic corticotropin-releasing hormone is expected in patients with congenital adrenal hyperplasia. Elevated levels are seen in patients with melancholic depression and anxiety disorders and have been considered a pathogenic mediator in such disorders (87). The incidence of these psychological disorders in patients with congenital adrenal hyperplasia needs to be studied.

The heterozygote state for 21-hydroxylase deficiency has been found in increased frequency in children with premature adrenarche (66). In a recent study of Greek children with premature adrenarche, the incidence of heterozygotic 21-hydroxylase gene mutations was 35% (67). We do not know the incidence of the congenital adrenal hyperplasia carrier state in women with hyperandrogenism, in men with testicular tumors, or in men and women with adrenal incidentalomas. We will need to determine whether and why such a mild defect is or may be associated with these conditions.

It is possible that a heterozygotic defect is subclinical in most instances but becomes apparent when it is associated with other defects in patients' genetic and constitutional backgrounds. A person who is heterozygous for congenital adrenal hyperplasia could also have genetically and constitutionally determined mild insulin resistance and a mild gene defect that makes her ovaries vulnerable to the polycystic ovary syndrome. The latter two states (insulin resistance and gene defect) may potentiate the effects of the heterozygosity on the adrenal glands, ovary, or both and lead to overt adrenal or ovarian hyperandrogenism manifested as premature adrenarche or the polycystic ovary syndrome (42). Thus, a single defect that is too small in itself to cause disease may do so when it combines with one or more defects of genes or functions with epistatic effects on its action.

What are the new avenues for treatment? A corticotropin-releasing hormone antagonist, in combination with glucocorticoid and mineralocorticoid therapy, could in theory obviate the need for an antiandrogen–aromatase inhibitor or bilateral adrenalectomy. Our early preclinical results with a corticotropin-releasing hormone antagonist are promising (19, 88, 89). Such an antagonist could be used until gene therapy becomes safe and effective. A prototype corticotropin-releasing hormone receptor antagonist, antalarmin, binds to corticotropin-releasing hormone receptor type I and blocks the effects of corticotropin-releasing hormone on that receptor (88). It acutely and chronically decreases corticotropin and cortisol secretion without causing adrenal insufficiency (19).

There is now convincing evidence from studies of the fetal adrenal gland in humans that corticotropin-releasing hormone of placental origin stimulates the secretion of androgens by the fetal adrenal zone (90). In the adult adrenal gland, the adrenomedullary sympathetic system, through such locally produced peptides as corticotropin-releasing hormone, stimulates the zona reticularis (42). It is therefore possible that antalarmin, acting also at the level of the zona reticularis, blocks the production of androgens by this zone, possibly adding further benefit. We are currently testing this hypothesis.

In the past 50 years, since the discovery of cortisone therapy as an effective treatment for congenital adrenal hyperplasia, many advances have been made in the study and management of 21-hydroxylase deficiency. The discovery of the 21-hydroxylase gene was followed by the discovery of the 21-hydroxylase–deficient mouse, which has provided a useful model in which to test new treatment approaches. As our knowledge of this disease expands, new therapies are being developed and tested in both humans and the animal model.

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Second Primary Colorectal Cancer: The Consequence of Management Failure at Several Potential Levels

Patients with previously diagnosed colorectal cancer are thought to be at increased risk for second primary large-bowel cancer (1–3). Widely endorsed surveillance guidelines promote regular colonoscopic evaluations after initial cancer resection in this high-risk group (4, 5). Given the generally accepted progression from adenoma to carcinoma, an effective surveillance strategy would identify and remove both preinvasive and early invasive neoplasms so that cancer might be prevented or detected before metastasizing. However, few data have been available to evaluate the effectiveness of current approaches to postoperative surveillance in reducing the risk for and from subsequent colorectal cancer.

In this issue, Green and colleagues (6) report their findings from a historical cohort study designed to determine the incidence of second primary colorectal cancer among patients with resected stage II or stage III colonic malignancies when intensive surveillance was attempted. The study involved 3278 patients who participated in a multi-institutional adjuvant chemotherapy trial (Intergroup 0089) (7). During 15 345 person-years of follow-up, the observed rate of second primary colorectal cancer was 274 cases per 100 000 person-years, a rate significantly higher than that expected based on data from either the Surveillance, Epidemiology, and End Results program (8) (standardized incidence ratio, 1.6 [95% CI, 1.2 to 2.2]) or the National Polyp Study (9) (standardized incidence ratio, 6.8 [CI, 2.7 to 22.0]). The authors concluded that the incidence of second primary colorectal cancer remains high despite intensive surveillance strategies. This alarming conclusion warrants careful scrutiny and should be assessed to determine potential explanations about how existing evaluation and surveillance strategies may be falling short.

MISSED SYNCHRONOUS CANCER

In the cohort studied by Green and colleagues, more than half of the 42 cases of second primary colorectal cancer (24, or 57%) presented within 2 years after initial cancer resection. Of these, most (17 of 24) were detected at the first postoperative examination. Such cancer was probably present when the initial cancer was resected (synchronous cancer), as the authors acknowledge. Rather than suggesting a deficiency in postoperative surveillance, missed synchronous cancer is more correctly ascribed to failures of preoperative and intraoperative evaluation. Meticulous care should be taken to exclude synchronous neoplasms during the baseline work-up for colorectal cancer so that consequent morbidity and potential death from additional surgery or tumor progression can be avoided. In this regard, further information from Green and colleagues' study (including completeness of the preoperative colorectal evaluation and location of any identified synchronous neoplasms) would have been helpful in determining appropriate corrective strategies. For example, newer technologies, such as computed tomography colonography (10), may allow effective examination of the more proximal colon when obstruction or angulation precludes the performance of complete colonoscopy.

NONADHERENCE TO SURVEILLANCE

It is difficult to assess the efficacy of a particular surveillance algorithm unless both patients and their physicians adhere to the recommended frequency and type of follow-up evaluations. Patients in the adjuvant chemotherapy trial reported by Green and colleagues (6) were to have received either colonoscopy or barium enema and flexible sigmoidoscopy 6, 12, and 18 months postoperatively and annually thereafter. At the discretion of each patient's physician, the interval between surveillance examinations could be extended to 18 to 24 months after the 6-month evaluation was completed. However, more than half of the patients who developed "incident" second primary colorectal cancer (diagnosed ≥2 years after resection) did not adhere to the intended surveillance protocol. The extent to which such a high nonadherence rate contributed to the incidence of subsequent colorectal cancer could have been explored by direct comparison with adherence rates in matched patients from the same trial who did not develop subsequent cancer. Nevertheless, given the low rate of adherence reported, it is difficult to impugn inadequacies in current surveillance guidelines as the major contributing factor in development of second primary colorectal cancer.

FALSE-NEGATIVE RESULTS ON SURVEILLANCE EXAMINATIONS

Among patients who adhered to surveillance guidelines in the report by Green and colleagues, most had had at least one colonoscopy. Colonoscopy is widely accepted as the gold standard for detecting asymptomatic colorectal neoplasia (11). Nonetheless, many factors can influence the quality of colonoscopy, including the adequacy of bowel preparation, level of instrument insertion, and examiner experience. Based on two recent studies that compared the results of repeated colonoscopies (12, 13), the false-negative rate for neoplastic polyps on colonoscopy ranges from 17% to 24%. Even if the colon is well prepared, neoplasms can evade detection because of location in blind areas, atypically flat configurations (14), or other factors. If second primary colorectal cancer is not recognized or not reached during an initial evaluation, it would be more appropriately attributed to perceptual error than to imprudent prolongation of the recommended surveillance interval.

AGGRESSIVE TUMORIGENESIS

According to the longitudinal data nicely documented by Green and colleagues, subsequent colorectal cancer clearly developed in 5 or 6 patients despite previous colonoscopic examinations performed at or near the assigned follow-up intervals. This small but important subset of patients may have had a more sinister variant of neoplasia that eluded surveillance. Previous authors have noted that hereditary nonpolyposis colorectal cancer syndrome, in which carcinoma appears de novo or the transition from adenoma to carcinoma seems markedly accelerated (15, 16), accounts for a sizable proportion of second primary colorectal malignancies that emerge despite regular surveillance (17, 18). Because of the aggressive tumorigenesis associated with hereditary nonpolyposis colorectal cancer syndrome, patients who meet clinical or laboratory criteria for this syndrome are typically advised to undergo more extensive colectomy at the time of the first operation and to commit to more intensive surveillance after surgical resection. Green and colleagues provide limited details about whether patients with hereditary nonpolyposis colorectal cancer syndrome or other high-risk conditions (such as familial adenomatous polyposis or inflammatory bowel disease) were excluded. However, given the heterogeneity referent to age alone among second cases of primary colorectal cancer, generalizations about surveillance outcomes based on these data must be made with caution.

Variability in both the thoroughness of baseline or follow-up examinations and the composition of study samples, as mentioned earlier, may account for differences in observed colorectal cancer incidence between surveillance studies. Such variability, rather than biological factors, could explain the striking differences in Green and colleagues' cohort and the reference group from the National Polyp Study. In the National Polyp Study (9), patients with newly diagnosed colorectal adenomas were recruited from seven centers after undergoing complete colonoscopy at baseline. Surveillance colonoscopies were performed in a high percentage of patients (80%), and diligent polypectomy resulted in an exceptionally low colorectal cancer incidence (5 cases over 8401 person-years of follow-up). In contrast, patients with stage II or stage III colorectal cancer in the cohort studied by Green and colleagues were recruited from 683 institutions after undergoing a presumed, but not always documented, clearing examination of the colorectum. Moreover, the frequency and extent of interval polypectomies are unknown. Therefore, comparisons between these groups may not be entirely relevant.

CONCLUSION

A significant proportion of second primary colorectal cancer represents a failure in patient management at several possible levels. Subsequent colorectal cancer may present postoperatively because synchronous neoplasms are missed at baseline, patients or their physicians do not adhere to follow-up guidelines, surveillance procedures yield false-negative results, or tumorigenesis is unusually aggressive. There seem to be multiple opportunities for implementing more effective intervention and improving clinical outcomes. Although the study by Green and colleagues chronicles a disturbingly high rate of second primary colorectal cancer in patients undergoing surveillance in an adjuvant chemotherapy trial, the junctures at which corrective measures are most needed cannot be precisely determined. For now, adherence to the existing consensus guidelines (4, 5) for postoperative surveillance seems warranted until convincing evidence to support alternative strategies becomes available.

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EDITORS' NOTES: A NEW *ANNALS* FEATURE

With this issue, we inaugurate a new feature, editors' notes. Our goal is to provide readers with a brief snapshot of original research articles. We will write a very brief statement to frame each study within the landscape of existing knowledge (Context); describe what the study adds to its field of inquiry (Contribution); and state what we think to be the main clinical, research, or policy implication. We may also use these notes to caution readers to go slowly in applying the findings of the study. The notes will accompany each Article and Brief Communication.

We hope that the notes will serve several purposes. First, they should provide easy access to each study's "bottom line" for readers who are in a hurry. Second, we hope that they will help to make *Annals* a livelier read. Finally, the editors have lived with these articles through several months of review, debate among ourselves, and discussions with the authors. We want you, the reader, to learn why we thought an article was important enough for us to publish it.

Please let us know what you think of this new feature.

Harold C. Sox, MD
Editor

LETTERS

The Editors welcome submissions for possible publication in the Letters section. Authors of letters should: • Include no more than 300 words of text, three authors, and five references • Type with double-spacing • Send three copies of the letter, an authors' form (see Table of Contents for location) signed by all authors, a diskette containing the letter, and a cover letter describing any conflicts of interest related to the contents of the letter.

Letters commenting on an *Annals* article will be considered if they are received within 6 weeks of the time the article was published. Only some of the letters received can be published. Published letters are edited and may be shortened; tables and figures are included only selectively. Authors will be notified that the letter has been received. If the letter is selected for publication, the author will be notified about 3 weeks before the publication date. Unpublished letters cannot be returned.

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Influenza: Prospects for Control

TO THE EDITOR: We read Couch's editorial on influenza (1) with interest. After extensively reviewing the literature and searching specifically for the efficacy of the influenza vaccine and the true incidence of influenza virus infection, we were struck by the lack of evidence-based data to support the current perceived status of annual influenza immunization and its impact on the incidence of influenza. Every fall, health care providers are bombarded by patients and the news media about the upcoming "flu season" and the status of the new vaccine. Yet, in most of the randomized studies we reviewed, the end points and applied statistical analyses did not always reflect documented influenza infection. Vague, nonspecific symptoms, such as number of days of febrile illnesses; upper respiratory tract illnesses, defined as sore throat associated with fever or cough lasting longer than 24 hours; or rate of hospitalization of elderly patients at risk, were used to determine incidence of infection (2–4). Such symptoms can hardly be construed as representing influenza since a wide variety of infectious agents can cause them, and it is likely that the incidence of influenza infection is overestimated (5).

Therefore, to more accurately determine the reduction in rates of hospitalization, illness, and mortality attributable to the influenza vaccine and the true incidence of influenza infections, studies should be designed to document the prevalence of influenza infection by using specific laboratory tests (such as direct fluorescent antibody assay and cell culture techniques), or by obtaining serologic levels before and at the end of the study period. Without this information, it is not possible to demonstrate an association between persons at risk and virologically proven cases of influenza. In addition, these data should help determine the cost–benefit ratio of the vaccine.

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IN RESPONSE: Drs. Mazza and Yale have identified the two kinds of studies that characterize proof of value for influenza vaccines. Efficacy studies constitute proof that influenza virus infection and infection-specific illness and its consequences are reduced among persons given vaccine, preferably in randomized, placebo-controlled studies. Such studies have been numerous since vaccines were first described (1–3). The second study type is one in which use of influenza vaccine in a population is followed by reductions among vaccinees of influenza-like illnesses or the consequences of these illnesses during periods in which influenza virus infection is prevalent. This type of study, which is called an effectiveness study, generally involves larger population groups than efficacy trials and circumstances in which accurate detection of every infection may not be feasible. Nevertheless, such studies are beneficial for assessing value, particularly in cost–benefit analysis, since use of vaccine as recommended must be beneficial for preventing illnesses during the period of prevalence of the infection. For example, if efficacy was demonstrated for a vaccine but influenza infections were replaced among vaccinees by a similar infection and illness caused by another respiratory virus, and acute respiratory illnesses or their consequences did not change, effectiveness of influenza vaccine would not have been demonstrated, and no cost benefit would have been realized.

It is preferable to have precise data on the efficacy and effectiveness of the influenza vaccine in the same clinical trial, but using the period of prevalence as a surrogate for infection provides useful estimates of effectiveness. It is the combination of both types of study performed many times over many years that provided the consensus for the value of influenza vaccines that supports vaccine recommendations. A thoughtful analysis by Hirota and coworkers (4) and a report on prevention of influenza by the Cochrane Collaboration (5) address both types of study. Because of the variability of influenza and influenza vaccines among different populations and circumstances, it is highly desirable to conduct studies on a continuing basis. Both efficacy and effectiveness studies are needed and, when possible, should be done simultaneously.

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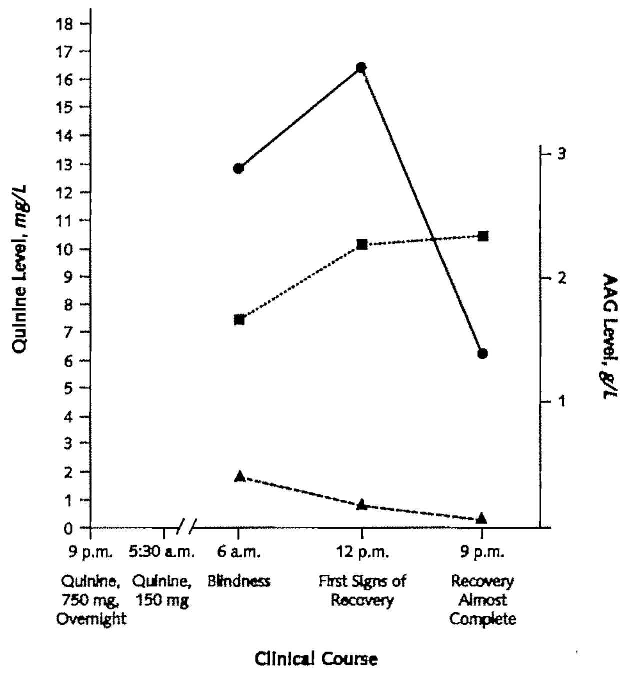
Quinine-Induced Blindness Reversed by an Increase in α_1-Acid Glycoprotein Level

TO THE EDITOR: In patients who have malaria and are receiving quinine treatment, blindness is an exceedingly rare event (<1 in 500 cases) whose pathogenesis is unclear (1). Since blindness has been more frequently associated with a total quinine intake of 4 g or greater, a concentration-dependent relationship seems plausible (2). We report the resolution of quinine-induced blindness in a patient with malaria whose total plasma quinine concentration at the start of recovery was unexpectedly higher than that measured when complete blindness was present.

A 43-year-old Ghanaian man residing in Italy presented with a mild malaria attack (9000 *Plasmodium falciparum* rings/µL; 0.2% parasitemia) 2 weeks after returning from a visit to Ghana. Because he was vomiting, he was treated with 750 mg of intravenous quinine (10 mg/kg of body weight infused over 5 hours), which was started at 9:00 p.m. A second quinine infusion of 750 mg was started at 5:30 a.m. the following day. At 6:00 a.m., the patient awakened and reported complete blindness. The infusion was immediately stopped. Ocular examination revealed fixed, dilated pupils; complete blindness; and normal fundi. Results of retinal fluorescein angiography, computed tomography of the brain, electroencephalography, and electrocardiography were normal. Six hours after blindness onset, the patient's sight began to improve. Color discrimination returned by mid-afternoon, and the following morning the patient was able to read and reported normal visual acuity. He was then treated with standard-dose sulfadoxine–pyrimethamine and made an uneventful recovery.

Figure. **Clinical course in relation to α_1-acid glycoprotein (*AAG*) level (*dotted line*), total quinine level (*solid line*), and unbound quinine level (*dashed line*).**



Quinine and α_1-acid glycoprotein (AAG) levels were measured over his clinical course (Figure). A reduced quinine clearance was apparent in our patient, since his quinine level was higher at 12:00 p.m. than at 6 hours previously despite interrupted infusion. During the same interval, from 6:00 a.m. to 12:00 p.m., the patient's AAG level increased by 37%. α_1-Acid glycoprotein is an acute-phase reactant. An increase in AAG level as part of the systemic inflammatory reaction associated with a malaria attack significantly reduces the fraction of unbound quinine because most of the drug is bound to AAG (3). Since therapeutic as well as toxic effects can be attributed to the unbound fraction of the drug (4), this mechanism can explain why our patient's sight began to improve when the total plasma quinine level was at its peak but the concentration of unbound quinine had decreased from 1.9 to 1.0 mg/L. Unusual patterns of drug disposition, such as inappropriate or delayed increases in AAG level, should be considered as possible individual determinants of quinine toxicity.

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BOOK NOTES

Structured abstracts of information on newly published books, computer programs, selected Web sites, and other material are provided in this portion of Medical Writings. "Order phone" numbers can be used to place orders directly with publishers.

Physicians' Cancer Chemotherapy Drug Manual 2001

Chu E, DeVita VT. 584 pages. Sudbury, MA: Jones and Bartlett; 2001. $56.95. ISBN 0763714488. Order phone 800-832-0034.

Field of medicine: Oncology.

Format: Spiral-bound softcover book and CD-ROM.

Audience: Oncologists and trainees in oncology, internists, family practitioners, and various health care professionals involved in the care of patients with cancer.

Purpose: To provide a practical reference on chemotherapeutic and biological agents in current clinical use for patients with cancer.

Content: The manual is divided into four chapters. Chapter 1 reviews the principles of chemotherapy that have been used in cancer drug development. Chapter 2 provides detailed monographs on individual chemotherapeutic and biological agents in current clinical use, presented in alphabetical order by generic name. There is a wealth of critical information on each agent: drug classification and category; mechanisms of action and resistance; aspects of clinical pharmacology and pharmacokinetics; clinical indications; drug interactions; and special considerations, such as toxicity. Chapter 3 covers the emetogenic and teratogenic potential of various agents and also provides recommendations for dose modifications in patients with myelosuppression or liver or renal dysfunction. Chapter 4 reviews the common multidrug regimens as well as single-agent regimens for solid tumors and hematologic malignancies.

Highlights: This handbook is well organized and easy to use. The information on chemotherapeutic and biological agents is also conveniently supplied on the CD-ROM that accompanies the handbook. Useful references are provided after chapters 1 and 4.

Limitations: A section devoted to the prevention and treatment of nausea and vomiting and of suspected or confirmed extravasation would have been helpful. Throughout the drug monographs, drugs with vesicant properties are described as "weak," "strong," or "potent" vesicants—potentially confusing terms not defined in the manual. An additional limitation among the drug monographs is inconsistency in descriptions of interactions with medications that are metabolized by the cytochrome P450 system or that inhibit the cytochrome P450 system. Some monographs list just a few examples, and some (for example, those on vincristine and vinorelbine) list none, stating only that the drugs should be used cautiously in patients receiving other drugs that affect the cytochrome P450 system.

Related reading: Other available handbooks include *Lippincott's Cancer Chemotherapy Handbook*, 2nd edition (Lippincott Williams & Wilkins, 2001); *Drug Information Handbook for Oncology*, 2nd edition (Lexi-Comp, 1999); and *Handbook of Cancer Chemotherapy*, 5th edition (Lippincott Williams & Wilkins, 1999).

Reviewers: Ellen F. Manzullo, MD, and Roger W. Anderson, DrPH, The University of Texas M.D. Anderson Cancer Center, Houston, Texas.

Writing, Speaking, and Communication Skills for Health Professionals

The Health Care Communication Group. 352 pages. New Haven: Yale Univ Pr; 2001. $17.95. ISBN 0300088620. Order phone 800-987-7323.

Field of medicine: Medical education and academic medical fields.

Format: Softcover book.

Audience: Residents, fellows, and junior faculty seeking an academic career and interested in improving skills in academic medical communication, including writing, speaking, and teaching.

Purpose: To provide practical solutions to many writing, speaking, and teaching problems that face junior members of the academic community.

Content: Five sections (consisting of 14 chapters) on reading science, writing science, speaking science, teaching science, and the business aspects of health care. Each chapter is written by a different author and covers topics from a practical perspective in a workshop-style format. Many chapters include practical tips and suggestions on issues such as sentence structure for grants, manuscripts, and abstracts; font size for poster presentations; and techniques for teaching learners with different learning styles. Additional chapters address broader topics, such as grant writing, setting up a medical practice, and interpreting medical literature.

Highlights: Each chapter can serve as an independent and concise reference. The writing style is informal and user-friendly. Clear examples fill the pages. Many suggestions are useful even for experienced faculty members.

Limitations: There is some redundancy across chapters, but this is a minor drawback, because many readers will read selected chapters. Some chapters consist mainly of lists with limited organizational structure. In general, little theoretical basis is given, although additional references are provided. The chapter on the creative writing process seemed inappropriate for highly structured, scientific writing.

Related reading: Several texts address technical writing, presentation skills, teaching, and communicating with patients, but none compile this breadth into one practical text. There are similar texts written for non-native English-speaking physicians, such as Mahler's *Medical Communication* (Univ of Michigan Pr, 1992). *Writing, Speaking, and Communication Skills for Health Professionals* is a valuable addition precisely because it is broad, yet concise, useful, and practical. Many budding academicians will benefit from this book.

Reviewers: Howard Schubiner, MD, and Susan Eggly, PhD, Wayne State University School of Medicine, Detroit, Michigan.

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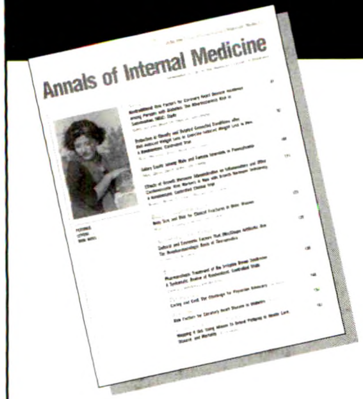

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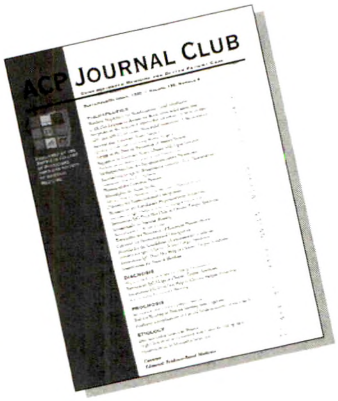

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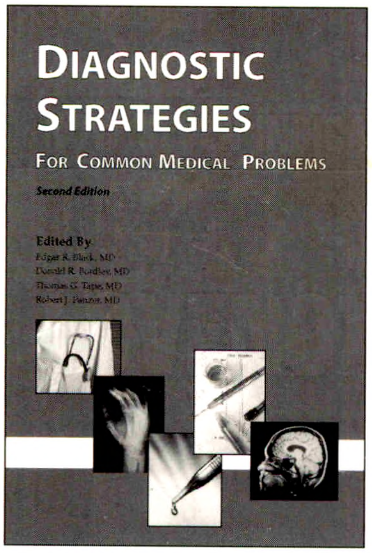

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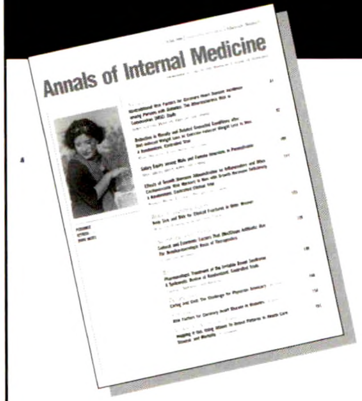

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V.L. Roger, S.J. Jacobsen, S.A. Weston, T.Y. Goraya, J. Killian, G.S. Reeder, T.E. Kottke, B.P. Yawn, and R.L. Frye

Over time, the incidence of hospitalized myocardial infarction decreased in men but increased in women and elderly persons. Survival benefits were clustered among younger persons. These results suggest that both incidence and survival contribute to the contrasting mortality trends by age and sex and that the burden of coronary disease has shifted toward elderly persons.

Survival Associated with 5-Fluorouracil–Based Adjuvant Chemotherapy among Elderly Patients with Node-Positive Colon Cancer 349

V. Sundararajan, N. Mitra, J.S. Jacobson, V.R. Grann, D.F. Heitjan, and A.I. Neugut

Adjuvant therapy with 5-fluorouracil is significantly associated with reduced mortality in older patients with node-positive colon cancer, similar to the association found in randomized, controlled trials among younger patients. More frequent use of this therapy in older patients would probably reduce the rate of death from colon cancer.

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T.D. Shanafelt, K.A. Bradley, J.E. Wipf, and A.L. Back

In this study, burnout was common among resident physicians and was associated with self-reported suboptimal patient care practices.

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Paying Research Subjects: An Analysis of Current Policies 368

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Acupuncture: Theory, Efficacy, and Practice 374

T.J. Kaptchuk

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Stress in Medical Residency: Status Quo after a Decade of Reform? 384

V.U. Collier, J.D. McCue, A. Markus, and L. Smith

Despite recent curricular reforms, an alarming number of current medicine residents report depressive symptoms, increasing cynicism, and decreasing humanism, which were associated with increasing educational debt and a need to moonlight for financial survival. Ongoing curricular reform, legislative relief from early loan repayment, and salary increases may be necessary to address these problems.

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L.H. Clever

Is burnout in residents a malignant disease? Do exhaustion, cynicism, and ineffectiveness start small, then grow, spread, and harm? If burnout in residents and other health professionals has been a silent but costly malignancy, the article by Shanafelt and colleagues in this issue makes a good start at exposing the problem.

Heeding the Plea To Deal with Resident Stress 394

J.J. Cohen

There is ample reason to be concerned about the health and welfare of today's medical residents. Indeed, data such as those presented by Collier and colleagues in this issue reconfirm what we have known for some time: The burdens that residents labor under are extracting an unacceptable toll on their well-being.

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S.L. Coyle for the Ethics and Human Rights Committee, American College of Physicians–American Society of Internal Medicine

This is part 1 of a 2-part paper on ethics and physician–industry relationships. Part 1 offers recommendations to individual physicians, mainly clinicians and clinician-researchers, about acceptance of gifts and other financial relationships with industry.

Physician–Industry Relations. Part 2: Organizational Issues 403

S.L. Coyle for the Ethics and Human Rights Committee, American College of Physicians–American Society of Internal Medicine

This is part 2 of a 2-part paper on ethics and physician–industry relationships. Part 2 addresses ethical concerns relevant to medical education providers, academic units that accept industry support, and medical professional societies.

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J. Coulehan

The guy's an iceberg. I feel the cold breeze the moment I walk into the office, where he stands beside the examining table, his arms crossed, a thin man, pale eyes, dour face, measured stare.

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The Appendix for the Information for Authors is published in the first issues of January and July. Please refer to the Appendix for information on manuscript format, style (manuscript typing and assembly), headings in text, style guidelines, title page, abstract, methods and results, discussion and conclusions, references, footnotes, tables and figures, acknowledgments, and current mailing address), and publication (scheduling of papers and proofs, ordering reprints, and complimentary copies).

Annals of Internal Medicine | ARTICLE

Trends in the Incidence and Survival of Patients with Hospitalized Myocardial Infarction, Olmsted County, Minnesota, 1979 to 1994

Véronique L. Roger, MD, MPH; Steven J. Jacobsen, MD, PhD; Susan A. Weston, MS; Tauqir Y. Goraya, MD, PhD; Jill Killian, BS; Guy S. Reeder, MD; Thomas E. Kottke, MD, MSPH; Barbara P. Yawn, MD, MSc; and Robert L. Frye, MD

Background: **Evidence indicates that deaths from coronary disease are decreasing less in elderly persons and women. Understanding the determinants of these trends is important for prevention.**

Objective: **To test the hypothesis that trends in incidence and survival of hospitalized myocardial infarction differ according to sex and age.**

Design: **Longitudinal observational study.**

Setting: **Community-dwelling persons in Olmsted County, Minnesota.**

Patients: **5117 patients who had an estimated 1820 incident myocardial infarctions from 1979 to 1994.**

Measurements: **Myocardial infarctions were validated by using epidemiologic criteria. Rates were directly adjusted to the age distribution of the 2000 U.S. population.**

Results: **Of the 1820 incident infarctions, 44% occurred in women and 36% in persons 75 years of age or older. In 1979, the age-adjusted incidence of myocardial infarction was 205 per 100 000 persons (95% CI, 162 to 247 per 100 000 persons). Between 1979 and 1994, the age-adjusted incidence of myocardial infarction decreased by 8% (CI, −23% to 10%) in men but increased by 36% (CI, 9% to 70%) in women. A 31% decrease in the incidence of infarction over time was observed in men 40 years of age compared with a 49% increase in women 80 years of age. Survival improved predominately in younger persons.**

Conclusions: **Over time, the incidence of hospitalized infarction decreased in men but increased in women and elderly persons. Survival benefits were clustered among younger persons. These results suggest that both incidence and survival contribute to the contrasting mortality trends by age and sex and that the burden of coronary disease has shifted toward elderly persons, a finding that has public health implications in an aging population.**

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Although age-adjusted mortality due to coronary disease had decreased in recent decades, the continuing burden of coronary disease should not be underestimated, and the determinants of this decrease have not been fully elucidated. Recent data from the United States indicate that the incidence of hospitalized myocardial infarction decreased modestly in recent years (1, 2), suggesting that medical care has contributed greatly to the decrease in mortality. Conversely, the World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease study conversely found that changes in incidence were the major reason for the decrease in deaths from coronary disease (3). These divergent findings warrant further analyses in different populations.

Moreover, because neither of these studies included persons older than 74 years of age, trends among elderly persons, the fastest growing segment of the population, could not be measured (1, 3–5). The Worcester Heart Attack Study showed that survival after myocardial infarction improved over time, but advancing age had a markedly adverse effect on survival (6). Although the explanations for these adverse findings are probably multifactorial and include more comorbid conditions and less use of efficacious therapies in elderly persons, these results emphasize the importance of monitoring coronary disease trends in this group.

Data from Olmsted County, Minnesota, for persons of all ages indicated that the decrease in coronary mortality affected primarily middle-aged men; this finding suggests that the burden of coronary deaths has been shifted toward women and elderly persons (7). These data further highlight the importance of including older age groups in studies and the need to elucidate age- and sex-specific mortality trends.

We sought to examine the trends in incidence and survival of patients with hospitalized myocardial infarction in Olmsted County, Minnesota. We tested two hypotheses: 1) that the incidence of myocardial infarction has not decreased overall over time, but that trends differ by sex and age, and 2) that survival after incident myocardial infarction has improved over time but that the magnitude of improvement differs by sex and age.

Context

Mortality from coronary disease and the number of people hospitalized for myocardial infarction have decreased in recent years. Medical care or reduced incidence of disease could be responsible.

Contribution

Between 1979 and 1994, age-adjusted incidence of myocardial infarction in Olmsted County, Minnesota, changed little overall, although it decreased 8% in men, increased 36% in women, and increased in older compared with younger persons. Mortality rates from myocardial infarction decreased in younger but not older persons.

Implications

Secular trends in myocardial infarction reflect changes in both incidence and survival and vary significantly with sex and age.

–The Editors

METHODS

Setting

Epidemiologic research in Olmsted County, Minnesota, is possible because the county is relatively isolated from other centers, and a few providers deliver nearly all medical care to local residents. The Mayo Clinic provides approximately half of the primary care and nearly all specialty care to the region, and Olmsted Medical Center and its affiliate Olmsted Community Hospital provide care for the region in every medical field. The characteristics of the Olmsted County population are similar to those of white persons in the United States overall, except that a higher proportion of Olmsted County residents are employed in the health care sector (8).

Each medical care provider uses a medical record system in which the details of every encounter are entered and can be easily retrieved; the Mayo Clinic has maintained extensive indices of clinical and histologic diagnoses and surgical procedures since the 1910s (9, 10). Since 1966, similar indices have been developed for non–Mayo Clinic providers through the Rochester Epidemiology Project, resulting in the linkage of medical records from all sources of care used by the population. This system provides a unique infrastructure for analyzing disease determinants and outcomes.

Enumeration of Hospitalized Patients with Acute Myocardial Infarction

Case Finding and Investigation

Lists of patients discharged from hospitals in Olmsted County who had diagnoses compatible with myocardial infarction were obtained from the Rochester Epidemiology Project index of diagnoses and the Hospital Utilization Review Database, an administrative database of hospitalizations maintained by the Mayo Clinic. The target International Classification of Diseases, Ninth Revision, codes were 410 (acute myocardial infarction), 411 (other acute and subacute forms of ischemic heart disease), 412 (old myocardial infarction), 413 (angina pectoris), and 414 (other forms of ischemic heart disease). All events coded as 410, a 50% random sample of code 411, and a 10% random sample of codes 412, 413, and 414 were reviewed. The sampling fractions were similar to those used in other studies (11).

Trained abstracters reviewed the medical records of Olmsted County residents and collected information on cardiac pain (defined as pain occurring in the anterior chest, arms or jaw, back, shoulder, or abdomen) and timing of its onset. Pain was categorized as present if it met these criteria and no other cause of pain could be determined (11). Creatinine phosphokinase values were transcribed for up to three measurements on each of the first 3 days after admission. Information on a potential history of trauma or surgery, which might invalidate enzyme values, was recorded.

Copies of up to three electrocardiograms (from the first day of the event or hospital admission, the last day of hospitalization, and the third day) were printed and sent to the Electrocardiogram Reading Center at the University of Minnesota to assign a Minnesota code (12).

Determination of Incident Status of Myocardial Infarction

The full medical record of each candidate case was searched for any episode compatible with previous infarction. Abstracters were asked to first examine the history surrounding the index event. If "no previous cardiac history" was specifically mentioned, the search for antecedent infarction was terminated. If a previous infarction was mentioned or if nothing was specified, all records before the index event were examined. If data were available, the possible antecedent event was validated by using the classification rule described below. If data were unavailable, the event was described qualitatively on the basis of the available documentation (confirmed by attending physician, history of "heart attack" according to the patient, mention of silent infarction without further descriptor, or mention of old infarction on physician's review of a routine electrocardiogram).

Classification of the Index Hospitalized Myocardial Infarction

Once the data for a hospitalized myocardial infarction were collected, a standardized classification rule was applied to assign an epidemiologic diagnosis (5, 11, 13). Cardiac pain was categorized as present or absent, and enzyme values were classified as abnormal, equivocal, or normal. When review by a physician-author confirmed a potential nonischemic cause of elevated enzyme levels, the classification was downgraded to equivocal.

According to the Minnesota system, one of five codes was assigned to the electrocardiograms (evolving diagnostic, diagnostic, evolving ST-T changes, equivocal, or absent). According to the classification rule, myocardial infarctions were classified as definite, probable, suspect, or no myocardial infarction on the basis of cardiac pain, enzyme, and electrocardiographic data.

According to published criteria (13), fatal myocardial infarction can be definitively diagnosed if the patient had a definite hospitalized infarction within 4 weeks of death or an acute infarction was found at autopsy. Of hospitalized persons with discharge codes 410 to 414, those who died in the emergency department, those who were dead on arrival, and those with in-hospital events with a rapid fatal course for whom no or little data were available were categorized as having infarction if they had an autopsy diagnosis of myocardial infarction.

Follow-up

In hospitalized patients, vital status was determined at discharge. Thereafter, it was determined by verification of death certificates, performed by the Rochester Epidemiology Project.

Reliability of the Myocardial Infarction Ascertainment Process

The abstracters were trained in methods for case finding and residency ascertainment through the Rochester Epidemiology Project. Quality control involved reabstraction of a random sample of 19 cases. The κ coefficient was used to evaluate interobserver variability for categorical variables. By convention, arbitrary categories were used to define poor ($\kappa \leq 0.4$), fair to good ($0.4 < \kappa \geq 0.7$), and excellent ($\kappa > 0.7$) agreement beyond chance. Categorical variables were history of myocardial infarction and cardiac pain. Agreement was excellent for history of infarction ($\kappa = 0.92$ ([95% CI, 0.79 to 1.0]), presence of cardiac pain ($\kappa = 0.93$ [CI, 0.84 to 1.0]), and presence of prolonged cardiac pain ($\kappa = 0.96$ [CI, 0.88 to 1.0]).

Statistical Analysis

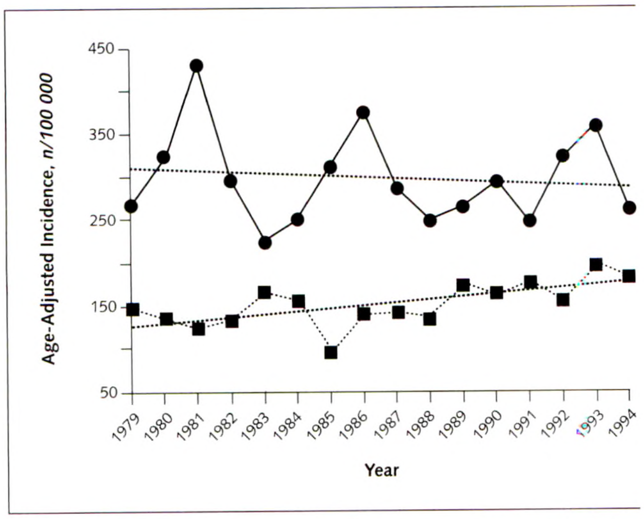
Age-, sex-, and year-specific incidences of hospitalized myocardial infarction were calculated. The numerators were the number of all definite and probable incident infarctions, and the denominators were the Olmsted County population as determined from census data for the years 1970, 1980, and 1990, with linear interpolation for the intercensus years and extrapolation after 1990 (14). Rates were directly adjusted to the age distribution of the 2000 U.S. population. Standard errors and 95% CIs were calculated on the basis of the Poisson error distribution.

Age- and sex-specific trends in the incidence of hospitalized myocardial infarction were assessed by using weighted Poisson regression. The analyses were weighted to avoid bias in the analysis of observations that were sampled with unequal probability of selection. Age- and sex-specific counts were used as the units of observation. Counts were based on 10-year age groups, and the midpoint of the age range was used as the value for age in the regression models.

Variables considered in the models were sex, calendar year, and age. The logarithm of the count was modeled, with the logarithm of the age- and sex-specific population size as the offset, by using S-Plus statistical software, version 3.4 (Insightful Corp., Seattle, Washington). Age and calendar year were entered as continuous variables. A linear and a quadratic component were tested for each variable, and the results of the final model were summarized by presenting the relative risk of incident myocardial infarction in 1994 compared with 1979 in selected age groups for men and women.

Time trends in 28-day case-fatality rates were analyzed by using logistic regression. Trends in long-term

Figure 1. **Trends in the incidence of myocardial infarction from 1979 to 1994 in Olmsted County, Minnesota, in men (*circles*) and women (*squares*).**



Incidence is shown on a linear scale and was adjusted by using the direct method to the age distribution of the total U.S. population in 2000. The heavy dotted lines represent the predicted values for the trends in incidence over time based on Poisson regression model.

survival were analyzed by using the Kaplan–Meier method and were compared with the expected survival of the Minnesota population. Proportional hazards modeling was used to examine the independent effect of year on survival while adjusting for age and sex. Comparison of the trends across age groups and between sexes was done by including interaction terms between year and age, and year and sex. A *P* value less than 0.05 was considered statistically significant, except when testing for interaction; in the latter case, *P* values up to 0.10 were considered significant.

RESULTS

Cohort

From 1979 to 1994, an estimated 1820 incident infarctions occurred in Olmsted County in 5117 patients screened. Data on health history before the index event available in the medical record covered a mean (±SD) period of 37 ± 19 years.

At the time of the index event, the median age was 69 years (interquartile range, 58 to 79 years). Forty-four percent of incident infarctions occurred in women, and 36% occurred in persons 75 years of age or older.

Trends in the Incidence of Hospitalized Myocardial Infarction

The overall age-adjusted incidence of hospitalized infarction changed little between 1979 and 1994: In 1979, it was 205 per 100 000 persons (95% CI, 162 to 247 per 100 000 persons), and in 1994, it was 218 per 100 000 persons (CI, 179 to 257 per 100 000 persons).

As shown by the Poisson regression models, trends over time in the incidence of myocardial infarction differed by age and sex. The incidence of infarction increased in women but decreased slightly in men ($P = 0.011$ for the time × sex interaction term) (**Figure 1**). Between 1979 and 1994, the age-adjusted incidence of myocardial infarction decreased by 0.5% per year in men, for a nonsignificant decrease of 8% (CI, −23% to 10%) over the study period. Conversely, in women, the age-adjusted incidence of myocardial infarction increased by 2.1% per year, corresponding to a statistically significant increase of 36% (CI, 9% to 70%) over the study period.

The incidence of myocardial infarction increased over time in older persons compared with younger persons ($P = 0.096$ for the time × age interaction term). **Table 1** shows the effect of age and sex, with some model-based calculations of relative risks. A 31% decrease in the incidence of myocardial infarction from 1979 to 1994 was observed in men 40 years of age, compared with a 49% increase in women 80 years of age.

Trends in Mortality after Hospitalized Incident Myocardial Infarction

Follow-up (mean duration, 5.1 ± 5.4 years) was 100% complete for mortality. The overall 28-day case-fatality rate remained greater than 10%, and no change was detected over time (**Table 2**). Similarly, no time trend was detected in each sex-specific stratum. The case-fatality rate decreased over time in persons younger

Table 1. **Age- and Sex-Specific Relative Risks for Incident Myocardial Infarction in 1994 Compared with 1979***

Age	Men	Women
40 years	0.69 (0.48–0.97)†	0.92 (0.68–1.54)
60 years	0.83 (0.67–1.02)	1.24 (0.96–1.60)
80 years	1.00 (0.78–1.28)	1.49 (1.16–1.92)†

* The referent is the corresponding age and sex stratum in 1979.
† $P < 0.05$.

Table 2. **28-Day Case-Fatality Rates for Incident Hospitalized Myocardial Infarction, by Tertiles of Time**

Group	Case-Fatality Rates for Incident Hospitalized Myocardial Infarction			P Value for Trend
	1979–1984	1985–1989	1990–1994	
	← % →			
Overall	12	13	11	>0.2
Men	10	9	7	>0.2
Women	14	20	15	>0.2
Age < 75 y	8	7	5	0.04
Age ≥ 75 y	19	24	22	>0.2

than 75 years of age (nominal P value = 0.04) but did not change in persons 75 years of age or older. After logistic regression and adjustment for age and sex, the direction of the association indicated a decrease in the case-fatality rate from 1979 to 1994 (odds ratio, 0.83 [CI, 0.50 to 1.39]; $P > 0.2$).

The 5-year survival rate after incident infarction was 64% (CI, 62% to 67%), which was significantly lower than the expected survival rate of 81% among the Minnesota population ($P = 0.001$) (**Figure 2**).

Proportional hazards regression indicated a decrease in the risk for death at all time points, but the magnitude of the effect of time differed by age ($P = 0.025$ for the year × age interaction term). The effect of age is further demonstrated by model-based calculations of relative risk for death after incident myocardial infarction in 1994 compared with 1979. In 1994, the relative risk for death was 0.45 (CI, 0.22 to 0.90) among persons 40 years of age, 0.70 (CI, 0.49 to 0.99) among persons 60 years of age, and 1.08 among persons 80 years of age (CI, 0.83 to 1.35); in the last group, the risk was unchanged from that in 1979.

Time Trends in the Use of Medications

From the first to the last tertile of the study period, the use of reperfusion therapy increased from 6% to 41% ($P < 0.001$). Similar increases were noted for use of aspirin at discharge (12% to 77%) and β-blockers at discharge (32% to 56%). Increased use of treatments over time did not differ by age or sex ($P > 0.10$ for age × year and for sex × year interactions).

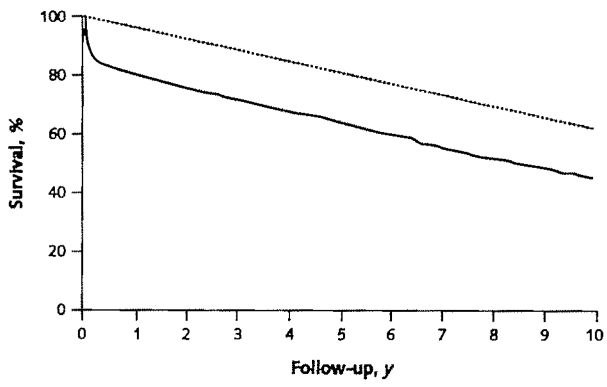
DISCUSSION

From 1979 to 1994, trends in the incidence of myocardial infarction in Olmsted County differed markedly by age and sex: During this time, an 8% decrease was observed in men but a 36% increase was observed in women. An increased incidence was also observed in older persons. The 28-day case-fatality rate and overall survival improved in younger persons, whereas they remained the same in older persons. These results indicate that the shift in coronary disease mortality toward women and elderly persons observed in Olmsted County during that period (7) is linked to age- and sex-based shifts in disease incidence and survival.

Myocardial Infarction Incidence

Recently published data from the World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease study (3) and the Atherosclerosis Risk in Communities study (2) underscore the complexity of coronary disease trends. The World Health Organization study ascribed the decrease in coronary deaths to changes in incidence, whereas the Atherosclerosis Risk in Communities study found mostly stable trends in myocardial infarction incidence despite decreasing mortality rates, suggesting that most of the decrease is related to improved medical care. However, neither of these two landmark studies included elderly persons, a growing segment of the population. Our study helps to elucidate this complex issue by demonstrating large age- and sex-based differences in secular trends of myocardial infarction incidence. A strength of our study is the avail-

Figure 2. **Observed survival after incident myocardial infarction in Olmsted County, Minnesota (*solid line*), and expected survival for the Minnesota population (*dotted line*).**



ability of almost 40 years of medical history before the index infarction, which is crucial to ascertaining the incident nature of the event.

The Worcester Heart Attack Study had no age limit for enrollment and showed a large decrease between 1975 and 1988 in the incidence of myocardial infarction among elderly persons but an increase in incidence among some age groups in women (15). Although qualitatively noteworthy, the exact magnitude and statistical significance of the age and sex differences in trends was not reported. Recent analyses from the Worcester Heart Attack Study indicated qualitatively flat trends in myocardial infarction incidence from the mid-1980s to the mid-1990s (16). No age- or sex-specific trends were reported.

Our results support and extend these data by showing large differences in the incidence of myocardial infarction between age- and sex-specific strata. The large decrease in incidence of myocardial infarction in younger men was of similar magnitude to the increase in incidence in older women.

Survival after Myocardial Infarction

Substantial improvement in survival after myocardial infarction among persons younger than 75 years of age during the second half of the 1980s, both in terms of the 28-day case-fatality rate (1, 2) and overall survival (1, 17), has been reported. The Worcester Heart Attack Study, which includes older persons, reported decreases in in-hospital mortality rates and adjusted long-term mortality rates (6, 16). Although these trends are encouraging, the decreasing length of stay may partially confound trends in short-term mortality after myocardial infarction if in-hospital mortality is used as the outcome measure. Furthermore, as indicated in the Worcester Heart Attack Study, age adversely affected survival, which necessitates adjustment for age in trend analysis. However, age-specific analyses are important to identify age groups in which the survival benefits may have differed. Our results extend those of previous reports by indicating that younger persons, but not older persons, experienced a large improvement in survival. Furthermore, although survival improved during a period of major advances in the treatment of acute myocardial infarction and chronic coronary disease, myocardial infarction continues to contribute greatly to reduced survival, compared with the expected survival in the same population; this reduction in survival occurs early after the infarction.

Implications of Secular Trends

The trends that we report are consistent with autopsy data from Olmsted County indicating a shift in the prevalence of anatomic coronary disease toward elderly persons (18). The consistency of these data strengthens the implications of the trends. The decrease in incidence of myocardial infarction among younger men suggests that primary prevention is effective among this group and highlights the need to revisit primary prevention measures in women and elderly persons, who have not experienced commensurate decreases. The improvement in survival observed in younger age groups is encouraging in terms of the effectiveness of therapeutic approaches to acute myocardial infarction and the effectiveness of secondary prevention. Yet, these trends contrast with a lack of noticeable survival benefit among older persons, which, combined with the trends in incidence, indicates a shift of the burden of coronary disease toward elderly persons. Because the population is aging, these unfavorable trends have major public health implications, and studies of possible explanations are needed. Reports of less use of thrombolytics in elderly persons (19) indicate that this pattern of care stems from clinical judgment that is appropriately based on comorbid conditions in some cases but only on older age in others, a practice that is not consistent with the published literature. Although ecologic analyses linking secular trends in therapies to trends in outcome are challenging, our study did not show that the increase over time in the use of reperfusion therapy and β-blockers and aspirin at discharge differed according to age. This in turn suggests that a differential increase over time in the use of these therapies is unlikely to fully explain the age differences in survival trends that we observed herein. Although some factors, such as delay in presenting to the hospital, can be addressed, other issues related to the risk-to-benefit ratio of aggressive management of acute myocardial infarction in the elderly are more complex (20).

Studies have documented age- and sex-based differences in the use of preventive services (21). Our data indicate that the effectiveness of secondary prevention programs in light of these secular trends should be investigated further.

Limitations

The racial and ethnic composition of Olmsted County limits generalization of our data to groups not adequately represented in the population studied. However, no population can be representative of the United States as a whole, as illustrated by the regional variations in heart disease rates observed in this country (22). The unique strengths of Olmsted County data reside less in their generalizability than in the ability to examine the various determinants of the decrease in deaths from coronary disease in a single population, from which incidence can be optimally ascertained because of the availability of longitudinal data.

Conclusions

In conclusion, between 1979 and 1994, the incidence of myocardial infarction decreased but increased substantially among women and elderly persons. Survival benefits are clustered among younger persons; no improvement could be discerned in older persons. These findings indicate that the burden of coronary disease is shifting toward elderly persons and suggest that preventive and therapeutic gains have not been experienced equally throughout the population. These trends have important public health implications in an aging population, and further studies of possible explanations are warranted to define preventive measures.

From the Mayo Clinic, Mayo Foundation, and Olmsted Medical Group, Rochester, Minnesota.

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AD LIBITUM

"So was I once myself a swinger of birches."
–"Birches"
Robert Frost

White Birch

I loved the tree before I knew its name
(As one may seek an unmet woman's eyes),
Its shade in summer, then when winter came,
Its stateliness in snow, its strength, its size.
Propped up against its trunk, I'd read or dream
Of faraway enchantments, or inflame
My mind with sultry sirens still unseen
But beckoning, as mythic songs proclaim.
I felt at home beneath that shady tree,
Anchored, engaged in life's incessant search—
King Arthur had Excalibur, for me
There was my rooted touchstone, my white birch.
When leaves are shed, its attributes remain—
I loved the tree before I knew its name.

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Survival Associated with 5-Fluorouracil–Based Adjuvant Chemotherapy among Elderly Patients with Node-Positive Colon Cancer

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Background: **Randomized clinical trials have demonstrated the efficacy of adjuvant 5-fluorouracil (5-FU)–based chemotherapy after surgical resection of node-positive colon cancer. Although this treatment became the standard in 1990 following a National Institutes of Health Consensus Conference, among those at least 65 years of age it is less likely to be offered to older or nonwhite patients.**

Objective: **To determine the association between 5-FU–based chemotherapy and survival in older patients.**

Design: **Retrospective cohort study.**

Setting: **Combined database of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and Medicare.**

Patients: **4768 patients 65 years of age or older who received a diagnosis of node-positive colon cancer from 1992 to 1996, were covered by Medicare Parts A and B, and resided in the population covered by the SEER program.**

Measurements: **Propensity scores to control for known predictors of receiving treatment, Cox proportional hazards models to assess the association of 5-FU therapy with survival, and sensitivity analyses to estimate the possible effects of unknown confounders.**

Results: **Fifty-two percent of patients received 5-FU therapy. For this sample, the hazard ratio for death associated with 5-FU therapy was 0.66 (95% CI, 0.60 to 0.73). Confounding could have accounted for this association only if an unmeasured confounder were extremely unequally distributed between the treated and untreated groups or increased mortality by at least 50%.**

Conclusions: **5-Fluorouracil adjuvant therapy is significantly associated with reduced mortality in older patients, similar to the association found in randomized, controlled trials among younger patients. More frequent use of 5-FU therapy in older patients would probably reduce death from colon cancer.**

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Since 1990, adjuvant chemotherapy with 5-fluorouracil (5-FU)–based regimens has been the standard of care for patients with node-positive colon cancer. In that year, Moertel and colleagues (1) reported the results of a phase III randomized, controlled trial in which patients who received 5-FU had a 41% lower recurrence rate and a 33% lower mortality rate (estimated) at 3 years compared with controls. Shortly thereafter, a National Institutes of Health Consensus Conference (2) acknowledged the benefits of 5-FU–based adjuvant chemotherapy for patients with node-positive disease. After a median follow-up of 6 years, the 5-year survival rate in the trial by Moertel and colleagues was approximately 70% in patients who received surgery plus chemotherapy and 50% among those who received surgery alone (3).

Nearly 75% of cases of colorectal cancer are diagnosed in patients older than 65 years of age (4), but most participants in randomized, controlled trials are younger than 65 years (5). If 5-FU–based adjuvant chemotherapy is efficacious in older patients, treatment of this subgroup could substantially reduce overall death from colorectal cancer. However, confirming estimates from an earlier study (6), we recently reported that only 52% of patients older than 65 years of age who had node-positive colon cancer had received 5-FU therapy (7, 8). No treatment was associated with older age, black ethnicity, a smaller number of positive lymph nodes, and more comorbid conditions (8).

Cooperative oncology groups are now making efforts to include older patients in trials. However, clinical trials should be based on analysis of relevant pretrial data, including laboratory data and, where available, observational data. Moreover, participants in clinical trials do not represent all patients who may ultimately become candidates for treatment, and trial treatment may differ from clinical practice once a trial drug becomes commonly used. For example, patients who are believed to have a high risk for treatment-related toxicity are generally excluded or exclude themselves from clinical trials. For these and other reasons, trial results may differ from actual treatment outcomes in everyday practice. Population-based data may provide valuable insights into the practical effectiveness of a treatment that cannot be obtained from a trial. The purpose of this study was

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Context

Adjuvant chemotherapy is standard care for patients with node-positive colorectal cancer, but older patients are less likely than younger patients to receive adjuvant chemotherapy for colorectal cancer.

Chemotherapy trials enrolled mostly patients younger than 65 years of age, so clinicians may be reluctant to prescribe chemotherapy for their older patients.

Contribution

In this population-based study of 4768 patients 65 years of age and older with node-positive colorectal cancer, 5-fluorouracil–based chemotherapy yielded survival benefits similar to those observed in younger patients.

These results remained robust in a careful sensitivity analysis.

Implications

Increased use of 5-fluorouracil–based adjuvant chemotherapy in older patients with colorectal cancer would probably reduce cancer-related mortality.

–The Editors

to assess the effect of 5-FU–based adjuvant chemotherapy on survival in a population-based sample of elderly patients with node-positive colon cancer.

METHODS

Data Sources

We used a database developed in 1993 by Potosky and colleagues (9) that links files of patients with cancer from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry with Medicare claims files. The SEER files provide information on tumor histology and location, disease stage, individual demographic characteristics, primary surgical and radiation treatment, and survival for cases of cancer occurring in approximately 14% of the U.S. population. The Medicare claims files contain extensive diagnostic, treatment, and cost data for patients covered by Medicare.

Sample Selection

In the linked SEER–Medicare database, 60 511 patients received a first diagnosis of primary colon cancer from 1992 to 1996. Of these, 52 490 were at least 65 years of age and 7659 had stage III disease (according to American Joint Cancer Committee criteria). We excluded 2622 patients who were enrolled in a health maintenance organization (HMO) from 12 months before diagnosis to 120 days after diagnosis and who were not covered by Medicare Parts A and B during the 16-month interval. The Health Care Financing Administration does not collect claims data from risk-based HMOs. We also excluded 13 patients who survived less than 120 days after the date of diagnosis; 39 patients who did not have positive regional nodes confirmed on pathologic examination and surgical resection of the tumor; and 23 patients with small-cell, squamous-cell, adenocystic, adenosquamous, or carcinoid tumors. Thus, 4962 patients, none of whom received a diagnosis at autopsy or from death certificate data, were included in our study.

Treatment with 5-FU–Based Adjuvant Chemotherapy

With national codes used by the Health Care Financing Administration, the Common Procedure Coding System (HCPCS), we identified patients who had received 5-FU (level II HCPCS code J9190) in their physician's office or at a hospital outpatient department. Those who began 5-FU therapy within 120 days of cancer diagnosis were classified as receiving adjuvant 5-FU treatment. For patients who did not receive 5-FU, we determined whether level II HCPCS codes or International Classification of Diseases, 9th revision, Clinical Modification diagnostic codes from physician claims files showed evidence of other chemotherapy.

Sociodemographic Variables, Comorbid Disease, and Determination of Survival

The SEER database includes data on age, ethnicity, sex, and area of residence. To assess the prevalence of comorbid disease in our cohort, we used the Deyo adaptation of the Charlson comorbidity index (10, 11). In its inpatient files, the Medicare database allows up to 10 codes from the International Classification of Diseases, 9th revision, Clinical Modification per admission. We searched all available codes to identify patients in the Medicare files who had a history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild to severe liver disease, diabetes with or without end-organ damage, hemiplegia, moderate or severe renal disease, or AIDS from 365 days before to 120 days after cancer diagnosis. Each category was weighted according to the Charlson index. For those who died by the end of follow-up on 15 April 1999, we determined survival time as the interval from the date of cancer diagnosis to the Medicare date of death. Those surviving past 15 April 1999 were classified as censored (alive at the end of follow-up), and the interval from their diagnosis date to the end of follow-up was included in the survival analysis.

Statistical Analysis

We used SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina), for all analyses. A Cox proportional hazards model was developed to compare survival in patients who received 5-FU therapy and those who did not. To balance observed covariates between the two groups, we used propensity score methods (12–14). Finally, to assess the extent to which an unmeasured covariate might explain our results, we conducted a formal sensitivity analysis (15).

Propensity Score Methods

Random assignment to treatment groups is a major feature of randomized, controlled trials. The purpose of randomization is to minimize systematic differences between treatment groups in the distribution of observed or unobserved covariates. Observational studies are generally considered less informative about treatment effects than randomized, controlled trials because, given the investigators' inability to randomize, the treated and control groups may differ considerably in baseline predictors of outcome. Stratification, matching, or model-based covariate adjustment may be used to control for these differences. However, these techniques can be applied to only a limited number of covariates; it is not feasible to match treated and untreated patients on more than a handful of potential confounders. Stratification is also of limited benefit because when the number of strata is large, some strata may contain only treated patients or only untreated patients, and model-based covariate adjustment is problematic when the distributions of the covariates in the two groups do not overlap substantially (12). We therefore used propensity score methods to minimize bias in our survival analysis of patients with colon cancer who did or did not receive 5-FU therapy.

The propensity score can be thought of as a measure of the likelihood that a patient will be treated solely on the basis of his or her covariate information (12–14). To determine the propensity score, a logistic regression model is constructed in which the dependent variable is the treatment group and the independent variables are predictors of treatment. The propensity score for each patient is his or her probability of being in the treatment group based on the logistic regression model. When patients are grouped into five strata on the basis of their propensity scores, the treated and untreated patients in each stratum are theoretically balanced with respect to potentially confounding covariates. Subclassification into five strata of propensity scores, or quintiles, is considered adequate to remove more than 90% of the bias resulting from each of the covariates (16).

We estimated propensity scores for each patient using a logistic regression model with treatment as the dependent variable and factors potentially associated with treatment as the independent variables. We then grouped the patients into five strata representing quintiles of the propensity score. In each quintile of propensity scores, we analyzed the association of treatment with mortality using a Cox proportional hazards regression model. We also modeled the association of treatment with death for the entire sample, controlling for propensity score and age as continuous variables. We then plotted survival curves for the treated and untreated groups, adjusting for propensity score and age (17).

Sensitivity Analysis

Like randomization, stratification on propensity scores balances the treated and untreated groups with respect to observed covariates. However, randomization also balances the groups with respect to unobserved covariates. In nonrandomized studies, an observed association between treatment and outcome may reflect the effects of unknown or unmeasured confounders (covariates that are associated with both treatment and outcome). The objective of a sensitivity analysis is to investigate the possible effects of such unmeasured confounders on an observed association (15, 18, 19). In our analysis, we investigated the effects of an unmeasured binary confounder on the hazard ratio for 5-FU,

Table 1. **Demographic and Clinical Characteristics of Patients with Node-Positive Colon Cancer in the SEER–Medicare Database***

Characteristic	Patients	Patients Treated with 5-FU
	n (%)	%
Age		
65–69 y	798 (17)	77
70–74 y	1172 (25)	72
75–79 y	1186 (25)	58
80–84 y	887 (19)	32
≥85 y	725 (15)	10
Year of diagnosis		
1992	1015 (21)	51
1993	944 (20)	51
1994	952 (20)	52
1995	977 (21)	53
1996	880 (19)	56
Ethnicity		
Non-Hispanic white	3992 (84)	53
Non-Hispanic black	372 (8)	43
Hispanic	167 (4)	53
Other	237 (5)	50
Sex		
Male	2044 (43)	57
Female	2724 (57)	48
Urban residence†		
Yes	3939 (83)	53
No	829 (17)	51
SEER registry site		
Los Angeles, CA	694 (15)	52
Atlanta, GA	262 (6)	54
Connecticut	737 (16)	56
Detroit, MI	757 (16)	57
Hawaii	123 (2.6)	46
New Mexico	167 (3.5)	48
Iowa	744 (16)	52
San Francisco, CA	423 (9)	44
San Jose, CA	211 (4)	47
Seattle, WA	460 (10)	49
Utah	190 (4)	53
Lymph nodes involved with tumor		
1	1679 (35)	50
2	959 (20)	49
≥3	1967 (41)	57
Unknown	163 (3)	47
Tumor grade		
Well differentiated	262 (6)	47
Moderately differentiated	2965 (62)	53
Poorly differentiated	1280 (27)	51
Undifferentiated	61 (1)	46
Unknown	200 (4)	55
Extent of disease		
T1	83 (2)	64
T2	344 (7)	55
T3	3953 (83)	52
T4	388 (8.1)	52
Charlson comorbidity score		
0	2901 (63)	59
1	1188 (26)	47
>1	532 (12)	33
Total	4768 (100)	52

* 5-FU = 5-fluorouracil; CA = California; GA = Georgia; MI = Michigan; SEER = Surveillance, Epidemiology, and End Results; WA = Washington.
† Population ≥250 000.

varying both the prevalence of the unknown confounder in the treatment and control groups and the relative hazard of death associated with the unmeasured confounder.

One unmeasured potential confounder in our data is the performance status or functional impairment of patients with cancer. The SEER–Medicare database does not include information about performance status. Performance status has been linked to cancer survival (20–23) and is also likely to be associated with the decision to treat with chemotherapy; the greater the degree of functional impairment, the less likely it is that a patient will receive chemotherapy. Therefore, an association of 5-FU therapy with survival may well be confounded by performance status. By conducting a sensitivity analysis, we were able to test the magnitude of the independent effect necessary for an unmeasured confounder to account for the observed association of treatment with survival.

Role of the Funding Sources

The U.S. National Cancer Institute and the American Cancer Society funded the study but had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Of the original group of 4962 patients with node-positive colon cancer, 194 (3.91%) received chemotherapy that did not include 5-FU. These patients were excluded from further analysis. **Table 1** shows the demographic and clinical characteristics of the remaining 4768 patients and the proportions treated with 5-FU. Overall, 52% of patients received 5-FU. **Table 2** compares treated and untreated patients with respect to age, year of diagnosis, ethnicity, sex, urban residence, specific SEER cancer registry site, number of lymph nodes involved with tumor, tumor grade, extent of disease, and comorbid disease status. All of these covariates were predictors of treatment with 5-FU and were unequally distributed between the treated and untreated groups. With adjustment for propensity score, all covariates (except for age) were balanced within each stratum. Only 11% of patients in quintile 1 (mean age, 87 years) but 83% of those in quintile 5 (mean age, 69 years) were treated (Table 3). Therefore, age was strongly associated with treatment.

Because age was still unequally balanced between the two treatment groups even after patients were stratified into quintiles of propensity score (Table 3), we controlled for age in our analysis of the survival benefit of 5-FU within each quintile. In quintile 1, treatment with 5-FU did not seem to be significantly associated with survival. In quintiles 2 through 5, treatment with 5-FU was associated with better survival (hazard ratios, 0.55 to 0.75). After evaluating all patients and controlling for age and quintile of propensity score, we found that treatment with 5-FU was associated with a mortality reduction greater than 30% (Figure).

Table 2. **Significance of Differences between Treated and Untreated Patients, before and after Propensity Score Adjustment***

Covariates	*P* Values for the Difference between Treated and Untreated Patients	
	Without Adjustment	With Adjustment
Age	<0.001	<0.001
Year of diagnosis	0.01	>0.2
Ethnicity		
Non-Hispanic white	0.003	>0.2
Non-Hispanic black	0.003	>0.2
Hispanic	>0.2	>0.2
Other	>0.2	>0.2
Male sex	<0.001	>0.2
Urban residence	0.08	>0.2
SEER registry site		
Los Angeles, CA	>0.2	>0.2
Atlanta, GA	>0.2	>0.2
Connecticut	0.027	>0.2
Detroit, MI	0.0019	>0.2
Hawaii	0.18	>0.2
New Mexico	>0.2	>0.2
Iowa	<0.001	>0.2
San Francisco, CA	0.14	>0.2
San Jose, CA	0.13	>0.2
Seattle, WA	>0.2	>0.2
Utah	<0.001	>0.2
Lymph nodes involved with tumor		
1	0.005	>0.2
2	0.02	>0.2
≥3	0.001	>0.2
Unknown	0.14	>0.2
Tumor grade		
Well differentiated	0.06	>0.2
Moderately differentiated	0.09	>0.2
Poorly differentiated	>0.2	>0.2
Undifferentiated	>0.2	>0.2
Unknown differentiation	>0.2	>0.2
Extent of disease		
T1	0.03	>0.2
T2	<0.001	>0.2
T3	0.20	>0.2
T4	>0.2	>0.2
Charlson comorbidity score	<0.001	>0.2

* CA = California; GA = Georgia; MI = Michigan; SEER = Surveillance, Epidemiology, and End Results; WA = Washington.

Table 3. **Association of Treatment with Age, and Rate Ratio for Mortality according to Propensity Score Quintile***

Quintile	Patients Treated, %	Mean Age (Range), *y*	Hazard Ratio (95% CI)†
1	11	87 (73–103)	0.81 (0.62–1.05)
2	38	80 (67–88)	0.55 (0.46–0.66)
3	59	76 (66–83)	0.64 (0.54–0.77)
4	74	73 (65–79)	0.75 (0.61–0.92)
5	83	69 (65–74)	0.71 (0.55–0.91)
Entire sample	52	76 (65–103)	0.66 (0.60–0.73)

* Propensity scores were calculated as the sum of the value of the coefficients for the variables multiplied by each patient's values for those variables in a logistic regression model of predictors of treatment. Quintiles represent patients grouped on the basis of propensity scores.

† Hazard ratios for the association of treatment with mortality within each quintile are adjusted for age; the hazard ratio for the entire sample is also adjusted for propensity score.

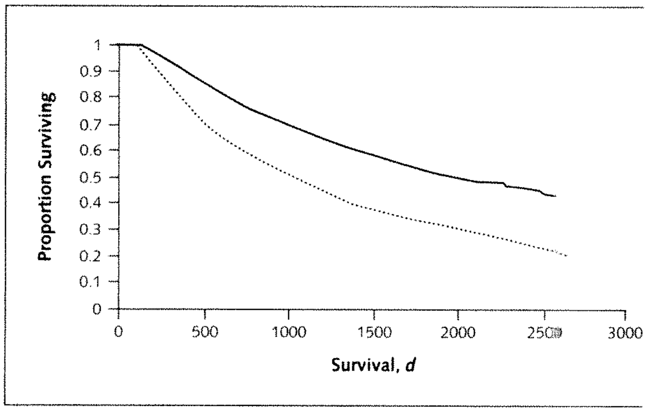
In sensitivity analyses (Table 4), we found that an unmeasured confounder would account for the observed association of 5-FU treatment with reduced mortality only if it were extremely unequally distributed between the treated and untreated groups or increased mortality by at least 50% (hazard ratio ≥ 1.5). For example, to account for the mortality reduction, a confounder would have to be nine times more prevalent in the untreated group and have a hazard ratio of 1.75, or be five times more prevalent in the untreated group and have a hazard ratio of 3.0.

DISCUSSION

In the past two decades, significant advances have been made in the prevention, early detection, and treatment of colon cancer in the United States. Although chemotherapy has not yet had a dramatic impact on the cure rate of advanced colon cancer, 5-FU therapy has been shown to be highly efficacious in reducing cause-specific mortality for node-positive disease and has become the standard of care (1–3, 24).

The *efficacy* of medical care denotes the benefits derived from treatment in the optimal environment of clinical trials, especially randomized, controlled trials. In these trials, researchers use special criteria to randomly assign participants to treatment and control groups that

Figure. **Survival of patients with node-positive colon cancer.**



The solid line indicates patients treated with 5-fluorouracil; the dotted line indicates those not treated with 5-fluorouracil.

are similar in the distribution of factors affecting response to treatment. Patients are selected for their performance status and ability to tolerate potentially toxic exposures (25). The process of care is maintained within specific guidelines, with frequent follow-up and protocols for subsequent disease management. However, in the "real world," physicians care for nonstandardized patients, and outcomes are determined by many uncontrolled or unknown factors, including variations in practice patterns and patient preferences. Therefore, the *effectiveness* of a treatment (that is, its benefit in everyday medical practice) may differ considerably from its efficacy.

Incidence rates for colorectal cancer are six times higher in persons 65 to 84 years of age than in younger persons. Age is also associated with stage at diagnosis and death; most deaths from colorectal cancer occur in persons older than 65 years of age (26). Although elderly persons bear most of the burden of cancer, older patients have been less likely to receive standard cancer treatments, even when such treatments are potentially curative. Studies of the use of potentially curative treatment for several types of cancer have found that the likelihood of not being treated increased with age (27–29). In a previous study, we found that increasing age had a strong inverse association with receipt of 5-FU–containing chemotherapy in patients with node-positive colon cancer (7, 8). A survey found that women with colorectal cancer who were older than 65 years of age were significantly less likely than younger patients to have been referred to oncologists and to have received radiation therapy or chemotherapy (30).

Clinicians may have good reasons for using less aggressive treatment in elderly patients with cancer. Elderly patients are more likely to have comorbid conditions or impairments of functional status that may make cancer treatment and its toxicities particularly difficult to tolerate. Chemotherapy for lung cancer (31) and radiation therapy for rectal cancer (32) have both been found to be more toxic in older than in younger patients. These considerations may account in part for the underrepresentation of elderly patients in clinical trials. However, a meta-analysis of 19 drug trials found no convincing evidence that chemotherapy was, in general, more toxic or less beneficial in patients 70 years of age or older than in younger patients (33). A secondary analysis of several phase II trials in patients with advanced cancer also found no evidence of increased toxicity in those older than 65 years of age (34); however, participants in these trials may have been selected because they had better than average overall health and functional status, regardless of age.

The SEER–Medicare database is well suited for studies of the effectiveness of treatment among elderly patients with cancer. Almost all persons older than 65 years of age are covered by Medicare, and Medicare claims files provide relatively detailed data on certain diagnoses and treatments. The database has limitations;

Table 4. **Sensitivity of the Hazard Ratio to an Unmeasured Binary Confounder***

Prevalence of UBC in the Untreated Group, %	Prevalence of UBC in the 5-FU Group, %	UBC Hazard Ratio	5-FU Hazard Ratio, Adjusted for UBC (95% CI)
50	10	3.00	1.11 (1.00–1.21)
60	10	2.00	0.96 (0.88–1.06)
50	10	2.00	0.90 (0.83–0.99)
90	50	2.00	0.84 (0.77–0.92)
90	10	1.75	1.03 (0.94–1.13)
90	50	1.75	0.81 (0.74–0.88)
50	10	1.75	0.85 (0.77–0.93)
90	10	1.5	0.92 (0.84–1.00)
90	50	1.5	0.77 (0.70–0.84)
50	10	1.5	0.79 (0.72–0.86)
90	10	1.25	0.79 (0.72–0.87)
90	50	1.25	0.72 (0.66–0.79)
50	10	1.25	0.73 (0.66–0.80)
90	10	1.1	0.72 (0.65–0.78)
90	0.5	1.1	0.69 (0.63–0.75)
50	10	1.1	0.69 (0.63–0.75)

* 5-FU = 5-fluorouracil; UBC = unmeasured binary confounder.

it does not contain data on oral prescription drugs, and it is not completely informative about treatments administered to hospital inpatients. However, 5-FU therapy is usually administered intravenously in outpatient settings.

Observational data cannot provide definitive evidence that treatment improves survival, because observational studies cannot fully control for the distribution of important covariates among treatment groups. However, propensity score methods allow researchers to control for a larger number of variables. Using these methods, we observed a significant improvement in survival in the treated group, with a hazard ratio of 0.66 overall (**Table 3**), and a fairly consistent benefit over the propensity score quintiles. The observed benefit was similar to that seen in randomized trials among generally younger patients. Sensitivity analyses also suggested that this observation is fairly robust and could be otherwise explained only by a highly unequal distribution of an unmeasured confounder. A recent meta-analysis involving 3361 elderly patients reported similar survival benefits (35).

The SEER database is the best-known source of population-based cancer data in the United States. Although the SEER database may underrepresent cancer incidence and mortality rates in less educated persons living in poorer and more rural areas, the difference between the SEER sample and the U.S. population in these variables rarely exceeds 5% (36). Therefore, the generalizability of our results to the U.S. population as a whole is probably strong.

Another strength of our study is the quality of the data themselves. The SEER data have been tested, quality controlled, and validated in several ways. In most evaluations of accuracy in representing diagnostic information, Medicare claims data for important diagnoses, such as myocardial infarction and diabetes, agree with data from chart abstraction more than 85% of the time (37, 38).

We believe that the HCPCS codes used to determine chemotherapy treatment status are accurate. Because oncologists must bill for the chemotherapy they deliver in order to be reimbursed, we doubt that the claims data underrepresent HCPCS codes for chemotherapy. In addition, because we performed iterative searches for chemotherapy codes, it is unlikely that we missed patients who received chemotherapy. A comparison of Medicare data with random chart reviews has confirmed the sensitivity and specificity of the chemotherapy data for 5-FU in patients with colon cancer (Warren J. Personal communication).

Our study has several limitations. The decision not to use adjuvant chemotherapy involves judgment on the part of the physician and the patient, and its appropriateness may not be measurable by reference to a medical claims data set. To assess comorbidity, we used hospital inpatient claims for conditions referenced in the Charlson comorbidity index (10, 11), but we had no data on performance status, which is known to be an important prognostic factor. We were also unable to determine whether oral levamisole or leucovorin was used because we had no data on oral medications.

The SEER–Medicare database does not include data on individual socioeconomic status or household size. Regardless of insurance coverage, socioeconomic status may be associated with treatment because poor patients may not be able to afford transportation or other amenities that make frequent outpatient visits for chemotherapy feasible. Older patients are more likely to live alone than younger patients, and having a spouse or other relative who can help with transportation or home care may also affect the feasibility of treatment. The SEER–Medicare database also excludes most patients younger than 65 years of age; therefore, we were unable to assess the prevalence of treatment among younger patients.

Our data set did not include patients who received a cancer diagnosis after 1996. In the past few years, several new chemotherapeutic regimens for colorectal cancer have come into use (39). Because these treatments have substantial toxicity, physicians may hesitate to offer them to older patients. Trials with survival end points are currently in progress for many of these new treatments. Assessment of quality-adjusted survival in younger and older patients will be of great value to physicians and patients confronting treatment decisions.

We excluded patients who had HMO coverage because we could not obtain treatment-specific data on them. Although our study sample may differ from the fee-for-service Medicare population, studies comparing HMO and fee-for-service patients with colon cancer have found few differences in care and no differences in outcomes in the Medicare setting (40) or elsewhere (41).

It is known that some patients decline chemotherapy because they fear its toxic side effects. However, in a survey among 20 patients receiving chemotherapy for colon cancer, patients rated their quality of life at 3.5 on a scale of 0 to 5 (0 = hospitalization, 5 = no modification) (42). The final report of the original trial of 5-FU and levamisole found that treatment reduced the recurrence rate by 40% and the mortality rate by 33% and did not cause detectable late side effects (3). A separate analysis found that 5-FU treatment was highly cost-effective, even with quality adjustment (43).

We examined patients 65 years of age or older who had node-positive colon cancer and found that survival was significantly greater in those who received 5-FU treatment. This difference is similar to that described in randomized clinical trials, and sensitivity analyses suggest that it is accurate and robust. Because most cases of colon cancer are diagnosed in patients older than 65 years of age, increased use of adjuvant 5-FU therapy among older patients with node-positive colon cancer would probably improve the overall survival of patients with colon cancer in the United States.

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Disclaimer: Although this study used the linked SEER–Medicare database, the interpretation and reporting of these data are solely the authors' responsibility.

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Burnout and Self-Reported Patient Care in an Internal Medicine Residency Program

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Background: Burnout is a syndrome of depersonalization, emotional exhaustion, and a sense of low personal accomplishment. Little is known about burnout in residents or its relationship to patient care.

Objective: To determine the prevalence of burnout in medical residents and explore its relationship to self-reported patient care practices.

Design: Cross-sectional study using an anonymous, mailed survey.

Setting: University-based residency program in Seattle, Washington.

Participants: 115 internal medicine residents.

Measurements: Burnout was measured by using the Maslach Burnout Inventory and was defined as scores in the high range for medical professionals on the depersonalization or emotional exhaustion subscales. Five questions developed for this study assessed self-reported patient care practices that suggested suboptimal care (for example, "I did not fully discuss treatment options or answer a patient's questions" or "I made . . . errors that were not due to a lack of knowledge or inexperience"). Depression and at-risk alcohol use were assessed by using validated screening questionnaires.

Results: Of 115 (76%) responding residents, 87 (76%) met the criteria for burnout. Compared with non–burned-out residents, burned-out residents were significantly more likely to self-report providing at least one type of suboptimal patient care at least monthly (53% vs. 21%; $P = 0.004$). In multivariate analyses, burnout—but not sex, depression, or at-risk alcohol use—was strongly associated with self-report of one or more suboptimal patient care practices at least monthly (odds ratio, 8.3 [95% CI, 2.6 to 26.5]). When each domain of burnout was evaluated separately, only a high score for depersonalization was associated with self-reported suboptimal patient care practices (in a dose–response relationship).

Conclusion: Burnout was common among resident physicians and was associated with self-reported suboptimal patient care practices.

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See related article on pp 384-390 and editorial comment on pp 391-393.

Burnout is a syndrome of depersonalization, emotional exhaustion, and a sense of low personal accomplishment that leads to decreased effectiveness at work (1). Burnout differs from depression in that burnout only involves a person's relationship to his or her work, whereas depression globally affects a person's life (1). A broad range of professions that share an intense involvement with people—including physicians (2, 3), nurses (4, 5), and educators (6)—experience burnout. Burnout is associated with decreased job performance (7) and reduced job commitment (5) and predicts stress-related health problems (8) and low career satisfaction (9, 10).

Burnout appears common among practicing physicians, with rates ranging from 25% to 60% (3, 10–14). However, only two small studies have described burnout in physicians during postgraduate residency training (15, 16). Moreover, no research has evaluated the potential relationship between physician burnout and patient care. We evaluated the prevalence of burnout among internal medicine residents in a single university-based program and evaluated the relationship of burnout to self-reported patient care practices.

METHODS

Participants

All residents in the University of Washington Affiliated Hospitals Internal Medicine Residency program (except the first author, who was a 3rd-year resident) were eligible for this study. Residents in the program graduated from 45 U.S. medical schools and 4 international medical schools; the cohort comprised residents in primary care and residents in categorical and preliminary internal medicine. The residents rotate through a university medical center, a Veterans Affairs hospital, and county and community hospitals. Fifty percent of their rotations include in-hospital on-call shifts. The University of Washington Human Subjects Institutional Review Board approved the study.

Data Collection

We mailed a 92-item, self-administered survey to residents' homes in February 2001. The survey ad-

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dressed topics in the following order: demographic characteristics; residency experience of work stresses; Maslach Burnout Inventory (MBI) (1); depression, at-risk alcohol use, and other substance abuse; patient care practices and attitudes; personal coping strategies to manage stress; the value of program features aimed at resident well-being; and career satisfaction. The accompanying cover letter stated that the purpose of the survey was to "better understand residents' feelings and identify what aspects of the residency are most stressful"; the letter also explained that participation was elective and that responses would be anonymous. Residents were blinded to any specific hypothesis of the study, and "burnout" was not mentioned in the cover letter. As an incentive to participate, residents who returned a separate postcard indicating that they had completed a survey were eligible for a drawing for a $100 gift certificate. After the survey was mailed once to all residents, two reminders were sent by e-mail.

Survey Measures

Burnout

The MBI is a 22-item questionnaire that has been shown to be reproducible and valid (1, 17–19) and is generally considered the gold standard measure for burnout (8). The inventory asks respondents to indicate on a 7-point Likert scale (which does not include the word "burnout") the frequency with which they experience certain feelings related to their work. The MBI evaluates three domains of burnout: 1) emotional exhaustion, which is measured with a subscale of 9 items (for example, "I feel emotionally drained from my work"); 2) depersonalization, which is measured with a subscale of 5 items (for example, "I've become more callous toward people since I took this job"); and 3) personal accomplishment, which is measured with 8 items (for example, "I feel I'm positively influencing people's lives through my work") (1).

On the basis of the MBI responses, independent subscale scores are calculated for each of the three domains of burnout. Low, average, and high scores for each domain are based on the low, medium, and high terciles of scores from a previously published study of 1104 medical professionals (1). For our study, we defined burnout as a high score on the depersonalization or emotional exhaustion subscales. We did not include the subscale scores for personal accomplishment in the criteria for burnout because previous research has suggested that this subscale measures a somewhat distinct dimension (1).

Context

Burnout, a syndrome of emotional exhaustion, depersonalization, and perceived low personal accomplishment, is common among practicing physicians.

The frequency and consequences of burnout among physician trainees (residents) are largely unknown.

Contribution

This survey from a single university-based training program showed that 76% of medical residents met criteria for burnout. Of these residents with burnout, 50% had depressive symptoms and 9% had at-risk alcohol use.

Burned-out residents more often reported career dissatisfaction (41% vs. 11%) and suboptimal patient care practices (53% vs. 21%) than residents without burnout.

Editor's Note

Useful information on burnout and renewal can be found at www.acponline.org/careers/catalog_resources.htm.

—The Editors

Self-Reported Patient Care Practices and Attitudes

For this study, we specifically developed eight statements describing self-reported practices (5 items) and attitudes (3 items) of patient care (**Table 1**). These statements were developed on the basis of hypothesized effects of burnout on patient care. In this report, we describe these items collectively as suboptimal patient care practices and attitudes; however, the questionnaire did not use this wording or explicitly indicate that these aspects of patient care were considered undesirable. The survey instructions asked residents to "rate how frequently you found yourself exhibiting the following attitudes or behaviors for any reason (time constraints, feeling rushed, need to leave hospital, etc.)." The response options were "never," "once," "several times per year," "monthly," and "weekly."

We constructed two summary measures for self-reported patient care practices. The first, more inclusive, summary measure was self-report of one or more suboptimal patient care practices reported monthly or weekly; this measure is hereafter called "suboptimal patient care practices at least monthly." A second summary

Table 1. **Self-Reported Characteristics of Participants**

Variable	Participants, *n* (%)
All respondents	115 (100)
Women	61 (53)
Married or partnered	63 (55)
Children	12 (10)
>1 year between undergraduate and medical school	48 (42)
Year of residency	
1	56 (48)
2	34 (30)
3	26 (23)
Maslach Burnout Index subscales*	
High score for depersonalization	74 (64)
High score for emotional exhaustion	61 (53)
Low score for personal accomplishment	36 (31)
Self-reported suboptimal patient care practiced at least monthly	
"I found myself discharging patients to make the service 'manageable' because the team was so busy."	41 (36)
"I did not fully discuss treatment options or answer a patient's questions."	10 (9)
"I made treatment or medication errors that were not due to a lack of knowledge or inexperience."	10 (9)
"I ordered restraints or medication for an agitated patient without evaluating him or her."	16 (14)
"I did not perform a diagnostic test because of desire to discharge a patient."	16 (14)
Self-reported suboptimal patient care attitudes experienced at least monthly	
"I paid little attention to the social or personal impact of an illness on a patient."	35 (30)
"I had little emotional reaction to the death of one of my patients."	21 (18)
"I felt guilty about how I treated a patient from a humanitarian standpoint."	15 (13)

* High depersonalization for medical professionals is a subscale score of 10 or higher; high emotional exhaustion for medical professionals is a subscale score of 27 or higher; and low personal accomplishment for medical professionals is a subscale score of 40 or higher (source, reference 1).

measure identified residents who self-reported one or more suboptimal patient care practices weekly. Residents identified by the second summary measure, which is hereafter called "suboptimal patient care practices weekly," are a subset of those identified by the first. We did not include the items for suboptimal patient care attitudes (**Table 1**) in these summary outcome measures because the suboptimal patient care attitude items were similar to items on the depersonalization subscale of the MBI and were therefore expected to be correlated with that subscale. Neither the individual questions about suboptimal patient care practices nor the summary measures have been validated.

Depression and Substance Abuse

We hypothesized that depression and substance abuse would be related to burnout and to self-reported suboptimal patient care attitudes and practices. The survey included a two-item screening questionnaire for depression that was developed as part of PRIME-MD (Primary Care Evaluation of Mental Disorders) (20) and that performs as well as longer screening questionnaires (21). Screening positive for depression was defined as answering "yes" to at least one of the two questions. This screening instrument has a positive likelihood ratio of 2.23 (95% CI, 1.98 to 2.50) for the diagnosis of current major depression and a negative likelihood ratio of 0.07 (CI, 0.04 to 0.15) (21). In addition, residents were asked whether they had had "major depression at any time in residency."

The survey included the three questions on consumption from the Alcohol Use Disorders Identification Test (AUDIT) (questions 1 to 3) to screen for at-risk alcohol use (22). To assess symptoms of alcohol dependence, we also included three additional AUDIT questions that pertained to 1) not fulfilling responsibilities because of drinking, 2) being unable to stop drinking, and 3) drinking in the morning (23). At-risk alcohol use was defined as self-report of 1) consuming 6 or more alcoholic drinks on at least one occasion per month (AUDIT question 3) or 2) having one or more symptoms of alcohol dependence in the past year. Question 3 on the AUDIT has a positive likelihood ratio of 11.00 (CI, 5.24 to 23.23) and a negative likelihood ratio of 0.48 (CI, 0.39 to 0.60) for heavy drinking or active alcohol abuse or dependence according to *Diagnostic and Statistical Manual of Mental Disorders*, third edition revised (DSM-IIIR) (22). By using the same comparison standard and data from the same validation study (unpublished findings), the screening test in our survey—which used questions about any symptoms of alcohol dependence in the past year combined with AUDIT question 3—has a positive likelihood ratio of 7.77 (CI, 4.29 to 14.06) and a negative likelihood ratio of 0.46 (0.29 to 0.62). To measure recreational use of other substances, such as 3,4-methylenedioxymethamphetamine (MDMA, also known as XTC or Ecstasy), we developed the following question: "How often do you use other recreational substances (marijuana, sedatives, stimulants, XTC, other)?" The response options were "never," "less than monthly," "monthly," "weekly," and "daily or almost daily." This question has not been validated.

Demographic and Other Participant Characteristics

We collected limited demographic information to ensure the anonymity of the respondents and to encourage participation and honest reporting (**Table 1**). The survey did not ask residents their age; however, as a proxy measure to identify older residents, one question asked whether the respondent had taken "a break more than 1 year between undergraduate work and medical school." To further protect anonymity, we obtained no information on the participants' specific training program (for example, transitional internship or categorical or primary care internal medicine residency) or current rotation site.

Residency Experience and Career Satisfaction

Other questions measured the level of stress that residents attributed to various aspects of their residency experience (14 items), the perceived value of personal coping strategies (8 items), and the perceived value of residency program features aimed at resident well-being (16 items). These questions, which were developed and tested before the surveys were distributed, have not been validated. Two questions were used to assess career satisfaction. Although these two questions have not been validated, they were based on questions previously used to study resident career satisfaction; thus, we can compare our data with those from previously published studies (10). The complete questionnaire is available from the authors upon request.

Statistical Analysis

Our initial analyses compared responses among the 1st-, 2nd-, and 3rd-year residents. Next, for all other characteristics, we performed bivariate analyses to compare residents who met criteria for burnout with those who did not. For the comparisons, all of which exclusively involved categorical variables, we used the chi-square test or Fisher exact test to determine statistical significance.

To evaluate whether burnout was independently associated with self-reported suboptimal patient care practices, we used forward stepwise logistic regression to control for measured demographic characteristics, responses to screening questions about depression, self-reported major depression during residency, at-risk alcohol use, and recreational substance use. In these multivariate analyses, we first modeled the odds ratio for self-reported suboptimal patient care practices at least monthly by comparing residents who met criteria for burnout with those who did not. Next, by using the same outcome measure, we constructed three forward stepwise logistic regression models in which each MBI subscale was evaluated as a dichotomous independent variable (for example, high and low depersonalization). Subsequently, we evaluated the three MBI subscales simultaneously in the same model. We then performed these multivariate analyses for the second summary outcome measure—self-reported suboptimal patient care practices weekly.

We conducted secondary analyses to evaluate differences between burned-out and non–burned-out residents in self-reported stressors, personal coping strategies, and the value of available program features aimed at helping residents with stress management. Chi-square or Fisher exact tests determined statistical significance.

The statistical software used for all analyses was SPSS, version 10.0.7 (SPSS, Inc., Chicago, Illinois).

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RESULTS

Of the 151 eligible residents, 115 (76%) returned surveys in February or March 2001. Participation decreased by residency year (the response rates were 90% among the 1st-year residents, 71% in 2nd-year residents, and 62% in 3rd-year residents; chi-square test for trend, $P = 0.001$). However, in bivariate analyses, resident responses to questions about burnout, depression, substance use, or patient care practices did not differ significantly by year of postgraduate training. Therefore, for the remaining analyses, we combined data for participants from all years of residency training.

Table 1 shows demographic data, MBI subscale scores, and self-reported suboptimal patient care practices and attitudes. Eighty-seven (76%) responding residents met criteria for burnout. The responding resi-

Table 2. **Resident Characteristics Hypothesized To Be Associated with Burnout**

Variable	Participants Who Did Not Meet Criteria for Burnout (*n* = 28)	Participants Who Met Criteria for Burnout (*n* = 87)	*P* Value
	n (%)		
Depression history			
Self-reported major depression during residency	3 (11)	27 (31)	0.031
Positive result on depression screening*	8 (29)	44 (51)	0.042
Substance use			
At-risk alcohol use†	2 (7)	8 (9)	>0.2
Monthly or weekly recreational drug use	0 (0)	3 (3)	>0.2
Career satisfaction			
Happy with career choice	25 (89)	51 (59)	0.003
Not sure would choose to become a physician again	2 (7)	23 (26)	0.031

* A positive result on this screening test is not equivalent to a diagnosis of current major depression. (Likelihood ratios are presented in the Methods section.)

† At-risk alcohol use was defined as self-reported consumption of at least 6 drinks on at least one occasion monthly or weekly ($n = 7$) or self-report of any symptom of alcohol dependence in the past year ($n = 7$).

dents had the following mean scores on the MBI subscales: for depersonalization, 12.7 (for medical professionals, a score ≥ 10 is considered high—indicating burnout); for emotional exhaustion, 26.4 (≥27 is considered high); and for personal accomplishment, 36.2 (this subscale has an inverse relationship to burnout, and a score ≤ 33 is considered low) (1).

Residents who met criteria for burnout were significantly more likely to report a break of more than 1 year between undergraduate and medical school (47% vs. 25%; $P = 0.039$). Rates of self-reported major depression and positive screening results for depression were also significantly increased among residents who met the criteria for burnout; career satisfaction showed a strong inverse relationship to burnout (**Table 2**). Other measured demographic characteristics or screening results for at-risk alcohol use or substance abuse (**Table 2**) did not significantly differ between residents who met criteria for burnout and those who did not.

Burnout and Self-Reported Suboptimal Patient Care Practices and Attitudes

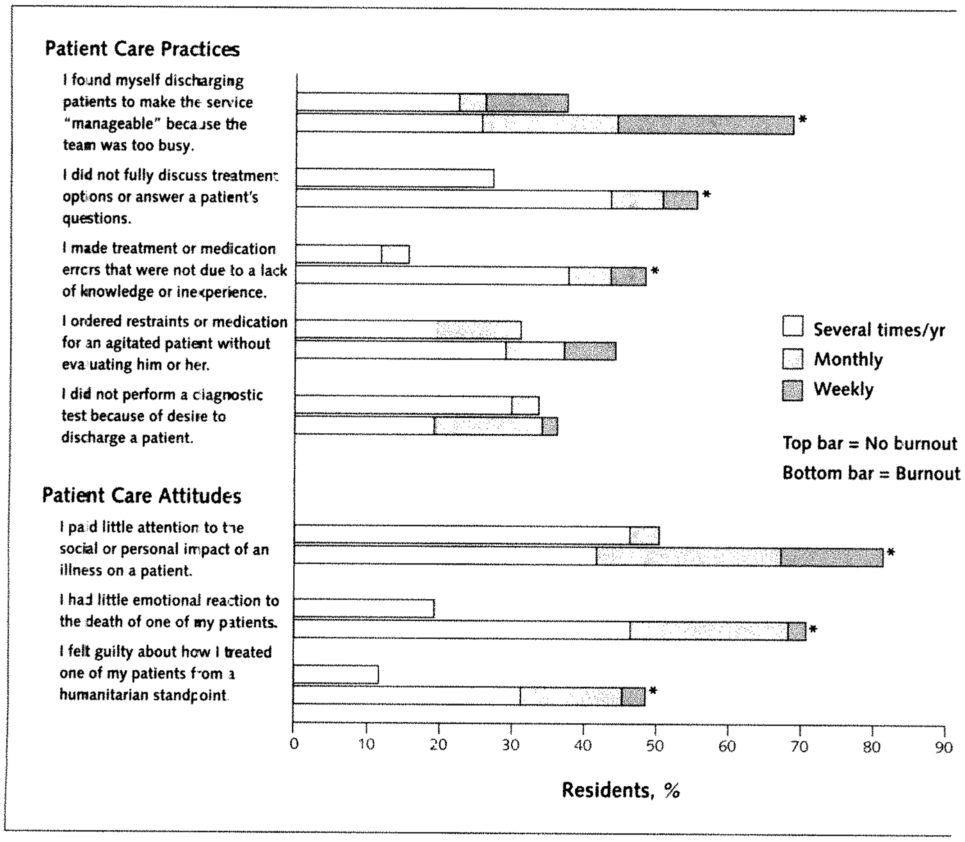
In bivariate analyses, residents who met the criteria for burnout were significantly more likely to report engaging in six of the eight suboptimal patient care practices and attitudes at least several times per year compared with residents who did not meet the criteria for burnout (**Figure**). Residents who met the criteria for burnout were also significantly more likely to report suboptimal patient care practices at least monthly (53% vs. 21%; $P = 0.004$) or weekly (32% vs. 11%; $P = 0.026$).

When we used multivariate logistic regression to evaluate the independent relationship between burnout and self-reported suboptimal patient care practices, burnout best predicted self-report of suboptimal patient care practices at least monthly (odds ratio, 8.3 [CI, 2.6 to 26.5]; $P < 0.001$). In these multivariate analyses, residents who reported a break of more than 1 year between undergraduate and medical school were less likely than other residents to report suboptimal patient care practices at least monthly (odds ratio, 0.3 [CI, 0.1 to 0.7]; $P = 0.008$), and 2nd-year residents were significantly more likely than 3rd-year residents to report suboptimal patient care practices at least monthly (odds ratio, 4.9 [CI, 1.4 to 16.8]; $P = 0.011$). No other measured characteristic—including sex, self-report of major depression during residency, positive result on depression screening, at-risk alcohol use, or substance abuse—was significantly associated with self-reported suboptimal patient care practices at least monthly. Only burnout significantly predicted suboptimal patient care practices reported weekly (odds ratio, 4.0 [CI, 1.1 to 14.2]; $P = 0.036$). No demographic or screening variable, aside from burnout, was significantly associated with self-report of suboptimal patient care practices weekly.

We evaluated each MBI subscale independently to assess its relationship to the two summary measures for self-reported suboptimal patient care practices. Only high scores on the depersonalization subscale were significantly associated with self-reported suboptimal patient care practices at least monthly (odds ratio, 5.8 [CI, 2.2 to 15.4]; $P < 0.001$) or weekly (odds ratio, 2.8 [CI, 1.1 to 7.7]; $P = 0.041$).

Because the threshold for a high depersonalization score had been defined somewhat arbitrarily (as a score in the top tercile among 1104 medical professionals [1]), we wondered whether the relationship between depersonalization and self-reported practices of suboptimal patient care reflected a threshold or a dose–response relationship. We therefore conducted secondary analyses to evaluate the odds of suboptimal

Figure. **Relationship of burnout to self-reported suboptimal patient care practices and attitudes.**



In each pair, the top bar represents residents who did not meet criteria for burnout ($n = 27$), and the bottom bar represents residents who met criteria for burnout ($n = 87$). The chi-square statistic compared residents who met criteria for burnout with those who did not on rates of each practice self-reported to occur at least several times per year. *$P < 0.05$.

patient care practices at least monthly among residents with depersonalization scores in each quintile (**Table 3**). In this fully adjusted model, we included quintile of scores for the MBI subscales as a categorical variable, with the lowest quintile as the referent category. Compared with residents whose depersonalization scores were in the lowest quintile, residents with depersonalization scores in the two highest quintiles were significantly more likely to report sub-optimal patient care practices at least monthly. This analysis also suggested a dose–response relationship: Increasing quintiles of depersonalization scores were associated with increasing odds of self-reported sub-optimal patient care practices at least monthly ($P = 0.014$ for depersonalization in quintiles overall).

Reported Stress and Relationship to Burnout

Secondary analyses explored relationships between burnout and resident reports of major stresses, personal coping strategies, and program features for managing stress. For the entire group of participating residents, the stresses most often rated as major were inadequate sleep (41%), frequently working shifts longer than 24 hours (40%), and inadequate leisure time (42%). Residents who met the criteria for burnout were significantly more likely to report each of these three stressors as major (for self-report of inadequate sleep or frequent shifts > 24 h, $P = 0.001$; for report of inadequate leisure time, $P = 0.012$); residents meeting burnout criteria were also significantly more likely to rate feeling uncertain about their future ($P = 0.042$) and feeling that their personal needs were inconsequential ($P = 0.031$) as major stressors.

The two personal coping strategies most often rated as "significant" or "essential" for managing stress, regardless of burnout, were talking with family or a significant other (72%) and talking with other residents or

Table 3. **Odds Ratio of Self-Reported Suboptimal Patient Care Practices, according to Depersonalization Score***

Quintile of Depersonalization Score	Odds Ratio of Self-Reported Suboptimal Patient Care Practiced Monthly or Weekly (95% CI)	P Value†
Lowest	1.00 (referent)	–
2nd	0.78 (0.19–3.13)	>0.2
3rd	1.51 (0.45–5.12)	>0.2
4th	4.00 (1.05–15.21)	0.042
Highest	4.96 (1.39–17.71)	0.014

* Data in the table were derived from a forward stepwise logistic regression model (as described in the Results section).

† For depersonalization (in quintiles) overall, $P = 0.014$.

interns (75%). Residents who met the criteria for burnout were significantly more likely to rate physical exercise ($P = 0.010$) and "a survival attitude" ($P < 0.001$) as "significant" or "essential" for managing stress.

Residents most often cited the following features of their residency program as being important for managing stress: having at least 4 days off per month (97%), receiving ancillary help (95%), and availability of a night-float (64%). Residents valued these features regardless of burnout. Residents who met the criteria for burnout were significantly less likely to rate the following program features as "important," "significant," or "essential": presentations on stress and the risk for depression ($P = 0.005$), constructive feedback ($P = 0.020$), and career counseling ($P = 0.003$).

DISCUSSION

To our knowledge, this is the largest published study of resident burnout and the only study to evaluate the relationship between physician burnout and measures of patient care. Burnout was very common among residents in all 3 years of residency training: More than 75% of respondents met the criteria for burnout. Burned-out residents were two to three times more likely to report suboptimal patient care practices at least monthly or weekly. In multivariate analyses adjusted for demographic characteristics and for responses to screening questionnaires for depression and substance abuse, depersonalization was the only dimension of burnout that was significantly associated with self-reported practices of suboptimal patient care. As we had expected, burnout was inversely related to career satisfaction.

Our study had several important limitations. Although the response rate was high, response bias remains a possibility, and the prevalence of burnout in this residency program could range from 57%, if all 36 nonrespondents were not burned out, to 87%, if all nonrespondents were burned out. We conducted our study primarily in February—a time of year during which resident morale is typically low and depression most common; therefore, surveying residents at a different time of year could have resulted in different rates of burnout. We could not compare respondents with nonrespondents because, to fully protect the anonymity of all residents (regardless of participation), we obtained only limited demographic information from respondents and did not seek review-board approval to obtain data on nonrespondents.

Our outcome measures for patient care practices were based on self-report, and we do not know the extent to which these self-reports accurately reflect the frequency of the five suboptimal patient care practices assessed in the survey. Although these questions have face validity, their criterion validity and reproducibility have not been studied. In addition, biased reporting of patient care practices could explain the observed relationship between burnout and patient care practices. For example, residents who met criteria for burnout could have over-reported suboptimal patient care behaviors. Alternatively, residents who were not burned out might

Table 4. **Comparison of Resident Burnout, according to the Maslach Burnout Index, in Published Reports**

Category on the Maslach Burnout Index	Internal Medicine Residents—Present Study (n = 115)	Family Practice Residents (n = 64)*	Internal Medicine Residents and Pediatrics Residents (n = 43)†
Average score for emotional exhaustion‡	26.4	25.3	28.5
Average score for depersonalization‡	12.7	12.2	14.0
Average score for personal accomplishment§	36.2	37.7	35.2

* Participants were in a community-based residency program (15).

† Participants were a convenience sample of residents from a university-based program who attended a workshop (16).

‡ A higher value indicates increased burnout.

§ A lower value indicates increased burnout.

have been more susceptible to social desirability bias; therefore, these residents could have under-reported their suboptimal patient care practices. However, other participant subgroups that might be expected to over-report suboptimal patient care practices or that could be less susceptible to social desirability bias—such as residents with positive results on depression screening or those with a low score for personal accomplishment—did not have increased rates of self-reported suboptimal patient care practices. Although we believe our results regarding the association between burnout and self-reported suboptimal patient care practices should be viewed cautiously and should be used primarily to generate hypotheses for future research, we doubt that these findings solely reflect biased reporting. Finally, this study is limited by its cross-sectional design. Future longitudinal studies are required to evaluate the possibility of a causal relationship between burnout and suboptimal patient care practices.

Neither sex nor responses on depression or substance abuse screening confounded the observed association between burnout and patient care practices. Likewise, because all respondents returned surveys in February or March, the time of year should not have confounded the relationship between reported burnout and patient care practices. However, we did not ask respondents about their current rotation site, workload, or on-call schedule. Such unmeasured potential confounders could explain the observed relationships between burnout and patient care and should be explored in future research.

Residents who met the criteria for burnout differed from other residents in their responses to several questions: the depression screening, major stresses, personal coping strategies, and program features considered valuable for managing stress. However, this cross-sectional study cannot assess whether any of these variables is causally related to burnout.

The generalizability of our results in this sample of residents from a single internal medicine program is unknown. However, we doubt that our results reflect unique characteristics of the residency program or residents studied. The mean scores that we observed for burnout are similar to those of two smaller studies in residents (**Table 4**) (15, 16). Moreover, the rates that we observed for positive results on depression and substance abuse screening are consistent with the findings of other reports on residents (24–30). Finally, residents in this program work in inpatient and outpatient settings that are typical for U.S. university-based training programs in internal medicine. For these reasons, it seems unlikely that our findings are unique to the program that we studied.

Our study has several important strengths. To our knowledge, our study is larger than previously reported studies of burnout among residents, and we had an excellent survey response rate (31). Residents were blinded to the purpose of the study. Although patient care outcomes were based on self-report, it seems likely that an alternate study design, by using directly observed behaviors as outcomes, could also reflect bias due to changes in resident behavior. Despite a relatively small study sample, our observed association between burnout and self-reported suboptimal patient care practices was statistically significant and large enough to suggest that the association of burnout with suboptimal patient care could be clinically meaningful. Moreover, our data suggest a dose–response relationship between depersonalization score and self-reported suboptimal patient care behaviors.

During the past 20 years, postgraduate physician training programs, including the one described in this report, have devoted increasing attention to improving the working conditions of residents (32–36). These programs are also working harder to identify impairment due to depression and substance abuse (34). This study suggests that burnout may be a type of resident impairment that is more prevalent than either depression or substance abuse and that resident burnout may be associated with suboptimal patient care. Previous studies of burnout in practicing physicians have shown that burnout can develop at any stage in the career of a physician (3, 10) and have linked burnout to physician satisfaction (3, 37), physician turnover (38), and physician resource use (39); however, no previous study has directly linked burnout to a measure of the quality of care. Given current national efforts to increase patient safety and patient involvement in health care (40) and to improve the quality of care (41), our findings suggest an important new research agenda regarding postgraduate medical education.

Resident burnout could contribute to the dehumanizing effects of medical education—especially for medical students, but also for other residents. Socialization of medical students has been described as a "hidden curriculum" in which students acquire attitudes and habits from other physicians (42). The high rate of burnout among residents, who spend far more time with medical students (43) and each other than with faculty physicians, raises the possibility that resident burnout influences what medical students and junior residents interpret as appropriate professional behavior. Burnout could contribute to increases in cynicism and decreases in compassion that have been previously observed over the course of postgraduate training (24, 32, 35, 44).

If future studies replicate our findings, increased understanding of the personal and programmatic factors that lead to burnout will be essential. Although this cross-sectional study could not assess the causes or prevention of burnout, resident perceptions of factors that increase and decrease stress may inform future research. Residents in this study most often cited workload as their major stress. This finding reinforces the importance of limits on workload and adequate time away from work. Other strategies to relieve resident and physician stress have been proposed and merit evaluation (16, 32, 36, 45). For example, one program found that a single 4-hour workshop teaching coping skills to residents improved burnout measured 6 weeks later (16).

Burnout appears to be common in residents and is associated with decreased resident well-being and career satisfaction. In addition, burnout is associated with self-reported patient care practices that are suboptimal. Further investigation of the prevalence, prevention, causes, consequences, and management of resident burnout is needed.

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Paying Research Subjects: An Analysis of Current Policies

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Background: **Few data are available on guidelines used by research organizations to make decisions about paying subjects.**

Objective: **To analyze existing guidance regarding payment of research subjects and to identify common characteristics and areas for further research.**

Design: **Descriptive content analysis of policies.**

Measurements: **Written policies and rules of thumb about paying subjects from 32 U.S. research organizations.**

Results: **Of 32 organizations, 37.5% had written guidelines about paying subjects; all but 1 reported having rules of thumb. Few (18.8%) were able to provide a confident estimate of the proportion of studies that pay subjects. Organizations reported that investigators and institutional review boards make payment decisions and that both healthy and ill subjects in some studies are paid for their time (87%), for inconvenience (84%), for travel (68%), as incentive (58%), or for incurring risk (32%). Most organizations require that payment be prorated (84%) and described in the consent document (94%).**

Conclusions: **Most organizations pay some research subjects, but few have written policies on payment. Because investigators and institutional review boards make payment decisions with little specific guidance, standards vary.**

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Clinical research would be impossible without the participation of willing human subjects. Research institutions are recruiting more participants more quickly than ever before (1). Some researchers consider payment crucial to recruitment, as evidenced by the sheer number of advertisements for paid studies in newspapers, on the radio, and on the Internet. Although paying research subjects is a common and long-standing practice in the United States (2), it remains contentious. Decisions about when, why, and how much to pay research subjects continue to spark disagreement within the research community.

Some have argued that paying subjects is unethical (3, 4), but most agree that it is acceptable in some cases. The prominent ethical concern is that money may unduly induce subjects to participate in research by compromising the voluntary nature of their decisions or their willingness to explore the risks and benefits of the study (5–7). Others worry that payment may target economically vulnerable persons or compromise scientific integrity by altering the makeup of the subject population. No empirical data exist on the validity of these concerns.

Federal regulations and guidelines provide minimal guidance on payment of research subjects. The U.S. Code of Federal Regulations never specifically mentions payment (8). *The Official IRB Guidebook* simply advises that the local institutional review board (IRB) should determine "whether the rewards offered for participation in research constitute undue inducement" (9). Information sheets from the U.S. Food and Drug Administration state that payment is not a "benefit, [but] a recruitment incentive" and advise IRBs to "review both the amount of payment and the method and timing of disbursement to assure that neither are coercive or present undue influence" (10). It is unknown how investigators or IRBs use these guidelines in designing and evaluating payment in research proposals.

Given the pervasiveness of the practice of paying research subjects, the disparate views on its appropriateness, and the sparseness of regulations, we examined and describe guidance that research organizations actively engaged in clinical research use to decide about payment of research subjects. Although alternate forms of "payment" raise similar ethical concerns (11), we focused on guidance regarding monetary payment of research subjects.

METHODS

The study included 32 geographically diverse organizations involved in the development, conduct, and review of biomedical research. We selected 12 academic research centers, 3 in each of the 4 census regions, from the 50 centers that receive the most funding from the U.S. Public Health Service; of these 12 centers, 9 agreed to participate. We contacted 20 of the largest pharmaceutical companies in the United States, and 7 agreed to participate; the others refused, citing the proprietary nature of the information. Eight of 12 contract research organizations (CROs) identified from the Centerwatch

Web site agreed to participate (12). Nine independent IRBs (freestanding, for-profit IRBs that review commercially funded as well as federally funded and community research) were identified from the Web site of the Health Industry Manufacturers Association (now called AdvaMed) (13), and 8 agreed to participate.

The project was explained over the telephone to the chair of the IRB, the vice president for research, or the equivalent person at each organization. Participation was requested, and a follow-up letter was sent. Data were collected in 1998 and 1999. We asked organizations to provide 1) the total number of clinical research studies initially approved in 1997; 2) the total number of studies that paid subjects in the same year; and 3) all organizational policies, guidelines, or rules of thumb regarding paying research subjects. Respondents were asked to send official copies of policies and guidelines (defined as written rules formally authorized by the organization) and to describe rules of thumb (defined as unwritten "rules" that had become standard practice at the organization) in a return letter. We clarified written submissions through follow-up telephone calls.

Responses were analyzed to determine the type of guidance used by the organization; descriptions of the purpose of payment; and specific requirements regarding advertising, informed consent, and determination of how much to pay subjects. We had previously identified these categories as important for analysis through literature review and discussion with IRB members, ethicists, and clinical researchers.

This study received IRB exemption from the Office of Human Subjects Research at the U.S. National Institutes of Health. Data are aggregated to protect the confidentiality of participating organizations. The Department of Clinical Bioethics, W.G. Magnuson Clinical Center, National Institutes of Health, funded the study, and members of the department were responsible for the collection, analysis, and interpretation of the data and the decision to submit the results for publication.

RESULTS

Thirty of 32 organizations paid subjects in at least some clinical studies that were initially approved during 1997. One organization reported no paid studies, and 1 could not determine whether any subjects had been paid. Few organizations (18.8%) were able to provide a confident estimate of the proportion of studies that paid subjects. Six of 9 academic research centers provided the total number of studies approved in 1997. Of these, only 4 had an electronic method of identifying paying studies; for the other 2 centers, we collected information from the cover page of the study description or from IRB minutes. At these 6 academic research centers, 23% of studies approved in 1997 offered payment to subjects.

Context

Many investigators pay research subjects. Paying research subjects could inappropriately influence them to participate in studies. We know little about how research organizations handle payment of research subjects.

Contribution

This survey of 9 academic centers, 7 pharmaceutical companies, 8 contract research organizations, and 8 independent institutional review boards showed that most paid subjects but few had formal policies to guide the amount or circumstances of payment.

Policy Implications

Without standard policies for paying research subjects, there are uncertain safeguards against unfair or coercive payment.

It is uncertain whether the organizations that participated are representative of all research organizations in the United States.

—The Editors

Most pharmaceutical companies and CROs could not provide the total number of studies approved in 1997 or provided it only for units that do phase I studies and pay almost all participants. Of 8 independent IRBs, 4 did not release the total number of studies approved because of proprietary reasons and none could determine the precise number of studies that paid subjects. However, 2 independent IRBs described the proportion of paid studies as "most" and 1 described it as "close to 80%."

Existence of Guidance on Payment

Only 37.5% of organizations (12 of 32) reported having written policies or guidelines about payment of research subjects. Three pharmaceutical companies reported having written guidance that applies only to phase I units and not to other studies that the companies support. In contrast, 31 of 32 organizations reported having unwritten rules of thumb. One pharma-

Table 1. **Content of Guidance on Payment to Research Subjects***

Specific Requirements for Payment Found in Policies or Rules of Thumb	Academic Research Centers (*n* = 9)	Pharmaceutical Companies (*n* = 6)	CROs (*n* = 8)	Independent IRBs (*n* = 8)
	← *n* →			
What to pay for				
Incentive	4	4	5	5
Time	7	6	6	8
Travel	6	5	5	5
Inconvenience	8	6	6	6
Risk	3	0	1	6
How to pay				
Specific formula	2	3	3	0
Prorating	8	5	5	8
Restrictions				
Completion bonus	5	4	4	5
Payment of patient-subjects	1	2	0	0

* CRO = contract research organization; IRB = institutional review board. Seven academic institutions, 3 pharmaceutical and biotechnology organizations, 0 CROs, and 2 independent IRBs had written policies or guidelines.

ceutical company with no written guidelines or rules of thumb reported that it leaves decisions about payment of subjects entirely to the site investigators and the IRB.

Participating pharmaceutical companies and CROs reported having little involvement with decisions about paying subjects in off-site studies. Study budgets are generally negotiated among sponsors, CROs, and study sites. Site investigators and staff typically determine the details of subject recruitment and payment, and the IRB is the ultimate arbiter in deciding whether a particular payment strategy is appropriate.

Content of Guidance

Guidance reflected wide variation in reasons for offering payment (**Table 1**). Slightly more than half of the organizations with payment guidelines or rules of thumb (58%) described payment as an incentive. Academic institutions, compared with the other three types of organizations, were least likely to do so (44% vs. 62.5% to 66%, respectively). Overall, most organizations said that subjects were paid for the time (87%), inconvenience (84%), or travel (68%) associated with research participation. Thirty-two percent reported that subjects were paid for incurring risk. Independent IRBs were more likely than other organizations to report that risk level affected payment decisions (75% vs. 0% to 33%, respectively). Notably, written guidance described payment almost exclusively as compensation for time and inconvenience. Half of the written guidelines explicitly stated that subjects should not be paid for risk, and only 4 of 12 written guidelines (33%) described payment as incentive for participation.

Only 8 of 32 organizations (2 academic institutions, 3 pharmaceutical companies, and 3 CROs) reported using a particular formula to calculate amount of payment (**Table 1**). For the 3 pharmaceutical companies and 3 CROs, the payment formula applies only to on-site phase I studies. Seven organizations with written guidance but no specific formula for calculating payment advise against excessive payment to avoid undue inducement; however, they do not specify what should be considered "excessive."

The eight formulas varied both in level of specificity and basis for calculating payment. Four organizations calculate payment for time by the hour, ranging from $4 to $10; the other four calculate payment per inpatient day or outpatient visit. Three of the organizations pay a flat rate per day or visit (range, $25 to $125) that is not altered for procedures performed during the study. Five organizations provide supplemental payment for procedures; of these, two specifically determine the supplemental amount according to the "inconvenience" of the procedure. No formula explicitly incorporates risk into determination of payment amounts. Only two pharmaceutical companies include formulas for calculating completion bonuses, which are predetermined lump-sum payments designed as incentives to finish a study.

Additional Requirements for How To Pay Subjects

Ninety percent of organizations reported paying healthy subjects and patient-subjects (persons who have the disease or condition under study) similarly when participation for each group involves similar procedures and no apparent difference in the likelihood of direct benefit. Only three organizations reported explicit restrictions on paying patient-subjects.

Most organizations (84%) require prorated payment (partial payment based on the amount of time or procedures actually finished) rather than payment that is contingent on completion of the study (Table 1). However, few organizations provide details on how to prorate. Three organizations consider the reason for subject withdrawal and pay the full amount of money to those who withdraw for medical reasons but a prorated amount to those who withdraw for nonmedical reasons.

Eighteen organizations (58%) reported rules on the use of completion bonuses (Table 1). Four prohibit completion bonuses, 2 use set completion bonuses for certain procedures or amounts of time, and 5 require that completion bonuses not exceed a certain percentage (25% to 50%) of the total. The other 7 organizations advise against excessive completion bonuses or allow them only for low-risk follow-up visits.

Specific Requirements for Informing Subjects about Payment

Twenty-nine organizations require IRB review of study advertisements (Table 2), which is consistent with the guidelines of the U.S. Food and Drug Administration (10); the other 2 organizations leave advertising decision to the study site. No organization completely prohibits mentioning payment in an advertisement, although 14 (48%) restrict the way in which such a mention can appear. Four organizations allow mention of payment but prohibit inclusion of the specific amount, 1 organization prohibits payment in advertisements for pediatric studies, and 1 organization prohibits listing a "theoretical maximum." Other organizations simply require that advertisements not "overemphasize" payment.

Most organizations require informed consent documents to contain the amount of payment subjects can expect (94%) and terms of payment (84%) (Table 2). Most (81%) also require that payment be described in a specific section of the document, usually a discrete section titled "payment for participation," "financial," "remuneration," or "compensation." Five organizations recommend including payment in the "benefits" section, and two specifically stipulate that it not be included in the "benefits" section.

DISCUSSION

These data suggest that standards for payment of subjects vary widely and that investigators and IRBs make decisions about payment with minimal guidance. We studied four major types of organizations that conduct and review human subjects research. Our data probably represent current practices across the country. Six findings are especially relevant.

First, many research organizations, surprisingly, have no systematic method of tracking how many of their studies pay subjects for participation. This makes it impossible to obtain an accurate count of paid studies. Information about payment to subjects, which would be relatively simple to add to existing databases, would not only help in analyzing the costs of subject recruitment

Table 2. **Requirements for Advertising and Informed Consent***

Specific Requirements for Informing Potential Subjects about Payment	Academic Research Centers (*n* = 9)	Pharmaceutical Companies (*n* = 6)	CROs (*n* = 8)	Independent IRBs (*n* = 8)
	←	*n*		→
Advertising				
Not addressed	0	1	1	0
IRB review required	9	5	7	8
Mention of payment prohibited	0	0	0	0
Mention of payment restricted	5	2	2	5
Informed consent document				
Not addressed	0	0	1	0
Mention of payment required	9	6	7	8
Specification of total amount of payment required	9	6	7	7
Specific terms of payment (for example, prorating) required	9	5	5	7
Specific section for payment required	6	5	6	8

* CRO = contract research organization; IRB = institutional review board.

but would also help gauge the pervasiveness of payment and the range of paying studies.

Second, IRBs seem to judge the acceptability and appropriateness of plans for paying subjects with little substantive guidance from sponsors, institutions, or federal regulations. Only 9 of the 17 IRBs sampled (7 academic and 2 independent) have written policies or guidelines with varied content. Most written guidelines simply caution against "undue inducement," but none describe how investigators or IRBs should determine when money is "undue." Little is known about the circumstances in which or the extent to which money inappropriately induces subjects to participate in research that is contrary to their interests. As Lemmens and Elliot observed, "it is no wonder that IRBs are baffled" (14).

Written guidance can contribute to standardization in an institution and assist persons involved in planning, conducting, and reviewing research (15). At the least, written guidance can articulate an organization's view of the purpose and nature of payment so that practices adhere to those values. This seems especially important given the demonstrated disagreement in the field over whether the purpose of payment is compensation for time, inconvenience, incentive, or risk. Written guidance can also provide a structure for calculating payment.

Third, few organizations, except pharmaceutical phase I units, have specific formulas for calculating payment. Rather, decisions tend to be made on the basis of each individual study. With no formula or statement detailing the purpose of payment, significant variation in payment among studies seems likely. Some may argue that there are too many types of studies to use a single formula. We recommend a model combining standardized payments for time with increases for inconvenient procedures and important follow-up visits (15). Amounts calculated with this model are generally moderate or low, minimizing the potential for undue inducement while simultaneously discouraging inadequate compensation. Such a model promotes standardization when studies are similar but allows flexibility when relevant differences exist, thereby minimizing competition between studies and adhering to a principle of fairness. While a specific dollar amount may be unworkable for some organizations, a structure for determining amounts (relationship to local wages, for example) would help to standardize payments in reasonable ways.

Fourth, most organizations require investigators to include detailed information about payment in a specific section of the informed consent document, separate from the risks and benefits of the study. Separating the description of payment from possible direct medical benefits of participation presents information to participants in an appropriately clear manner, thus facilitating informed choice.

Fifth, almost all respondents reported paying patient subjects and healthy subjects similar amounts when their participation involves similar procedures and no apparent difference in the likelihood of direct medical benefit. Although some have argued that patients and healthy subjects should be treated differently with respect to payment (16, 17), most organizations do not make an inherent distinction. We believe that treating subjects similarly when they play similar roles makes good ethical sense (15). Some argue against paying patients because patients derive medical benefit from research participation or may be especially vulnerable. Although many studies offer patients the prospect of direct benefit, others are conducted for purely research purposes and require a similar contribution of time and effort from both patient and healthy groups (for example, magnetic resonance imaging done solely to examine structural joint differences between patients with rheumatoid arthritis and healthy persons). While patients may be vulnerable in the context of clinical research, it is not clear that payment aggravates that vulnerability. In fact, payment may help patients distinguish procedures that are done purely for research purposes from those done for their benefit, thus minimizing vulnerability due to "therapeutic misconception" (15, 18).

Finally, although most respondents require prorated payment for subjects who do not complete a study, few have rules about prorating or about whether to consider subjects' reasons for withdrawal. Prorated payment recognizes the actual time and effort a subject contributes to research and is less likely to pressure a subject into completing a study or concealing information in order to receive money. This simultaneously guards the integrity of scientific data and the safety of human subjects.

Our study has limitations. First, our sample of 32 organizations is small. Second, our findings are limited in their application to pharmaceutical companies because of low participation from this group. However, academic institutions and independent IRBs seem to make most of the decisions about paying subjects, and both responded at a very high rate and make up a geographically diverse sample.

Our data illustrate several common practices regarding payment of human subjects that may represent benchmarks in the field. Of course, mere convergence does not make standards ethical, nor does variation imply a problem. However, knowing how conscientious organizations approach a difficult issue can aid in developing one's own approach. Our data also highlight several areas of variation that deserve further attention. Organizations should develop mechanisms for tracking studies that pay subjects, as well as written guidance about subject payment to guide their investigators and IRBs. Lack of a clear statement of the purpose of payment and a standardized way to determine acceptable amounts seems likely to lead to wide variations in practice and inconsistent judgments, even within an institution. Finally, most existing guidance discusses the need to minimize undue inducement. Further study and discussion are needed to understand when money is an undue influence, as well as the impact of payment on subject selection and scientific integrity.

Disagreement remains about the acceptable circumstances and manner in which to pay subjects for research participation. We hope that these data will stimulate discussion about appropriate practices within the research community and help organizations continue to evaluate and refine their own policies and practices.

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Acupuncture: Theory, Efficacy, and Practice

Ted J. Kaptchuk, OMD

Traditionally, acupuncture is embedded in naturalistic theories that are compatible with Confucianism and Taoism. Such ideas as *yin–yang, qi, dampness,* and *wind* represent East Asian conceptual frameworks that emphasize the reliability of ordinary, human sensory awareness. Many physicians who practice acupuncture reject such prescientific notions. Numerous randomized, controlled trials and more than 25 systematic reviews and meta-analyses have evaluated the clinical efficacy of acupuncture. Evidence from these trials indicates that acupuncture is effective for emesis developing after surgery or chemotherapy in adults and for nausea associated with pregnancy. Good evidence exists that acupuncture is also effective for relieving dental pain. For such conditions as chronic pain, back pain, and headache, the data are equivocal or contradictory. Clinical research on acupuncture poses unique methodologic challenges. Properly performed acupuncture seems to be a safe procedure. Basic-science research provides evidence that begins to offer plausible mechanisms for the presumed physiologic effects of acupuncture. Multiple research approaches have shown that acupuncture activates endogenous opioid mechanisms. Recent data, obtained by using functional magnetic resonance imaging, suggest that acupuncture has regionally specific, quantifiable effects on relevant brain structures. Acupuncture may stimulate gene expression of neuropeptides. The training and provision of acupuncture care in the United States are rapidly expanding.

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Acupuncture is an important therapy in East Asian medicine (the traditional medicine of China, Japan, and Korea). Treating headache by placing pins in the hands or treating asthma by placing needles in the feet challenges modern biomedical understanding. Thirty years ago, most physicians considered acupuncture a Chinese equivalent of voodoo. Despite the strangeness of its theory and method, in a very short period, acupuncture has changed from a cultural curiosity to an alternative therapy that, at a minimum, deserves a respectful hearing. This essay reviews the historical and theoretical framework of acupuncture, the scientific evidence for its claims to effectiveness, and its safety profile. The essay also discusses the provision of acupuncture therapy.

HISTORY

The earliest health care in China involved shaman-like rituals to placate spirits or demons (1, 2). At the same time, during the first few centuries BC, when philosophical systems such as Confucianism and Taoism were significantly replacing earlier Chinese supernatural thinking, acupuncture and other associated practices began to supplant antecedent magico-religious healing approaches (3, 4). China's emerging philosophies required a new medical system, free of supernatural thought and compatible with "naturalistic," human-centered presuppositions.

The precise origin of acupuncture techniques is a subject of scholarly debate. A "multilinear development toward acupuncture" seems likely (2). Early awareness of practical, needle-like therapy that used bamboo or bone needles to open abscesses may have contributed to the development of acupuncture (2). Knowledge of exact body locations (now considered acupuncture points) found in nondecorative tattoos on Stone Age mummies suggest another precursor route (5). The earliest Chinese archeologic textual material points to the existence of methods of heat stimulation (see following discussion) at precise regions of the body (which are clearly related to acupuncture channels) before any needling of acupuncture sites occurred (6). Another possible origin of acupuncture may be the bloodletting described in the earliest acupuncture sources. Bloodletting was originally used for "magical" healing, but by the time of the early acupuncture literature, it was being used for "naturalistic" reasons at acupuncture points based on Chinese medicine theory (7). Whatever the exact pathway may have been, by the time East Asian medicine was codified at some time in the first century BC (in a canonical text known as the *Inner Classic of the Yellow Emperor*), acupuncture was already a signature therapy of Chinese medicine.

BASIC THEORY AND CONCEPTUAL FRAMEWORK

From the Chinese perspective, acupuncture is necessarily embedded in a complex theoretical framework that provides conceptual and therapeutic directions. Un-

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like the earliest Chinese healing, which relied on supernatural guidance or altered states of consciousness, classic Chinese medicine relies on ordinary human sensory awareness. Its fundamental assertion, like the kindred philosophical systems of Confucianism and Taoism, is that contemplation and reflection on sensory perceptions and ordinary appearances are sufficient to understand the human condition, including health and illness. This assertion is fundamentally different from the biomedical viewpoint, which gives privileged status to objective technology and quantitative measurement. Ideally, the scientific analysis penetrates beyond the visible "life world" of the patient, revealing an underlying pathophysiologic disruption, independent from human subjectivity (8).

Despite acupuncture's claim to be based on ordinary perceptions, it is full of strange concepts that can act as formidable barriers (or attractions) to many Westerners. In fact, the foreign-sounding key words of acupuncture—for example, *yin, yang, dampness, wind, fire, dryness, cold,* and *earth*—are ordinary images or patterns (some culturally unique) of a person's state of being and behavior. They represent human "meteorologic" conditions, which are sometimes pathologic and disruptive and sometimes necessary and healthy. They are the fundamental patterns for detecting and synthesizing clinical information. These patterns also create a unique medical thought process.

Yin–Yang

Yin and yang are the basic root intuitions of China. They are recognizable in images akin to weather. Yin is associated with cold, darkness, being stationary, passiveness, receptivity, tranquility, and quiescence. Yang is associated with heat, light, stimulation, excess, assertiveness, dominance, movement, arousal, and dynamic potential. These complementary opposites are successively intertwined for additional levels of descriptive refinement.

A simple example is *dampness*. It has the yin qualities of cold, wet, soft, and lingering and also the yang qualities of excessiveness, dominance, heaviness, and "inexhaustible abundance." Acupuncturists claim that dampness is easy to recognize and that it applies to "psychological, ecological, and even moral as well as corporeal phenomena" (9). Some damp signs point to imbalance, or "bad weather," for example, weeping eczema, edema, "slippery" pulse, heaviness in digestion, indecision, clinging, or being helpful to others at the expense of oneself. Some dampness is an essential component of a healthy state of being, for example, smooth skin, normal secretions and excretions, being imperturbable when threatened, generosity, and patience.

In addition to a general synthesis, yin and yang and their climatic subcategories are used to interpret specific subregions of a person's health. These subregions can be different from a person's general meteorologic pattern and can create overlapping domains of yin and yang (for example, yins within yangs) that are as complex as multiple, intersecting circles. Both for the overview pattern and for the subregions, no single sign is conclusive; the overall context defines the parts. Heaviness in digestion or generosity might be "wind" if it appeared in a different configuration of signs. Unlike western medicine, in which signs and symptoms are used analytically to isolate an underlying mechanism, East Asian medicine seeks to discern a *qualitative image* in the overall gestalt or regions of a person's signs and behaviors. Whereas biomedicine aspires toward the scientific and dimensionally measurable *quantitative*, East Asian medicine emphasizes a human-centered approach of artistic impressions and sensitivities (10). If Chinese medicine resembles anything in the West, it would be the prescientific but rational Greek humoral medical system, which also perceived health status in such images of weather as phlegmatic (cold-moist) and choleric (hot-dry) (11).

Qi

In traditional acupuncture, the connection between such diverse phenomena as edema and generosity is explained by *qi* (pronounced "chee"). Qi is the linkage in the cosmos that, like the Greek notion of *pneuma*, takes myriad forms. The concept of qi has little scientific cogency, but for the Chinese, it provides a rationale for explaining change and linking phenomena. This rationale unites objective and subjective phenomena and locates disorders in the broadest context of a person's life (12). Whether qi is some kind of "real" quantitative energy in the western sense (akin to 19th century vitalist life-force notions [13]) or a metaphoric way of depicting and experiencing interconnection is not a serious intellectual issue in classic Asian thought (14).

In addition, the target of treatment in Chinese medicine is the state of "disharmony," any imbalance in yin–

yang and its connecting qi. It is not an abstract diagnosis or "truth" existing independent of the patient. A Chinese diagnosis can be compared to a practical "weather report" to guide the practitioner's response to the overall configuration of a patient's life.

ACUPUNCTURE THERAPEUTICS

Imbalances in yin–yang and qi need to be dynamically harmonized. Acupuncture is used to shift a person's unique "climate." It can moisten, dry, cool, warm, augment, deplete, redirect, reorganize, unblock, stabilize, raise, or lower a person's weather patterns. Fine needles are inserted into precisely defined, specific points on the body to correct disruptions in harmony. Heat stimulation, a technique known as *moxibustion*, which burns the herb *Artemisia vulgaris* near the acupuncture point, is sometimes used (especially to warm or move the qi). Hand pressure ("acupressure") is also sometimes applied. Classic theory recognizes about 365 points, said to be located on 14 main channels (or meridians) connecting the body in a weblike interconnecting matrix. These channels are not detectable by ordinary scientific methods (15). Additional acupuncture points (both on and off the channel) have been added through the millennia, and the total universe of points has increased to at least 2000 (16). In practice, however, the repertoire of a typical acupuncturist may be only 150 points. Traditionally, each acupuncture point has defined therapeutic actions; some points treat an entire yin–yang emblematic configuration, whereas others affect local symptoms. Between 5 and 15 needles are used in a typical treatment, with the point combinations varying during a course of sessions.

China, Japan, and Korea have each developed a distinct version of acupuncture. Thousands of years of history, interpretation, and innovation have produced multiple approaches (17). Specialized acupuncture has also been developed for the ears, scalp, and hands (18). Western nations have developed their own traditions, and one can begin to speak of French (19), British (20), and even American styles of acupuncture (21).

Biomedically trained physicians have developed acupuncture variants that reject "the metaphysical explanations and the necessity for mystical rituals" (22). Their approach emphasizes using acupuncture points based on western understanding of myofascial trigger points, the nervous system, or recent scientific discoveries about the likely mechanism of acupuncture (23). Some approaches used in ancient as well as modern times use standardized "formularies" involving a fixed menu of consistent points for a particular patient's symptoms, independent of traditional diagnosis. Although more philosophically compatible with biomedicine, these approaches are not entirely disassociated from traditional knowledge. Whether such approaches produce superior clinical results remains to be determined (24).

ASSOCIATED THERAPIES

Acupuncture is often used in conjunction with other modalities. Chinese herbal interventions, which can include animal parts and minerals in addition to botanicals, have historically been the mainstay of East Asian therapy. Although the Chinese materia medica includes more than 5000 entries (25), most practitioners rely on fewer than 250 substances. A body of biomedical literature on Chinese herbal pharmacology, pharmacokinetics, clinical efficacy, and associated adverse events is emerging, and the interested reader can find extensive information elsewhere (1).

Historically, acupuncturists consider the patient–physician relationship and therapeutic encounter itself to be inherently "potent" and sufficient to promote healing (1). In addition, acupuncturists use physical methods, such as massage, cupping (placing vacuum suction over point areas) (26), and scarification (counter-irritation) (27). Lifestyle counseling in such domains as diet, exercise, and mental health is also a component of acupuncture care. Modern *qi-gong*, which is sometimes used by acupuncturists, is a recent healing technique that combines older health and longevity practices (such as breathing and meditation practices) with an amalgam of Chinese religious ideas (28).

SCIENTIFIC EVALUATION OF ACUPUNCTURE

Clinical Evidence

Since the early 1970s, when acupuncture began to capture the popular imagination of the West, almost 500 randomized, controlled trials (RCTs) have evaluated its efficacy (29, 30). More than half were placebo-controlled trials, and the remainder pragmatically compared acupuncture or acupuncture plus conventional care with routine conventional treatment. A growing number of systematic reviews and meta-analyses that use stringent inclusion criteria has begun to synthesize this

Table 1. **Systematic Reviews and Meta-Analyses of Randomized, Controlled Trials of Acupuncture for Pain-Related Conditions***

Condition	Study (Reference)	Year	RCTs, *n*	Patients, *n*	Findings	Conclusions
Chronic pain	Patel et al. (31)	1989	14	720	Overall and in most subgroups pooled: positive; for acupuncture placebo trials: negative	Potential bias precluded conclusive findings, but most results were positive
Chronic pain	ter Riet et al. (32)	1990	51†		24 positive and 27 negative; for acupuncture vs. placebo trials: 15 positive and 17 negative	Highly contradictory evidence; efficacy remains doubtful
Chronic pain	Ezzo et al. (33)	2000	51	2423	21 positive and 27 negative; acupuncture was worse than control in 3 trials	Inconclusive evidence for acupuncture being more effective than placebo or standard care
Chronic neck and back pain	Smith et al. (34)	2000	13	522	All placebo-controlled: 5 positive and 8 negative; most valid trials tended to be negative	No convincing evidence for analgesic efficacy in chronic neck and back pain
Back pain	Ernst and White (35)	1998	12	591 (377 pooled)	9 studies pooled: odds ratio of improvement for acupuncture vs. control, 2.30; for placebo trials, 1.37	Acupuncture superior to various controls, but insufficient evidence to conclude whether superior to placebo
Low back pain	van Tulder et al. (36)	1999	11	542	No evidence that acupuncture was better than no treatment; moderate evidence that acupuncture was not more effective than TENS and trigger-point injection; limited evidence that acupuncture was not more effective than placebo	Effectiveness remains unclear
Osteoarthritis	Ernst (37)	1997	13†	437	Most trials had methodologic flaws	Highly contradictory evidence
Osteoarthritis of the knee	Ezzo et al. (38)	2001	7†	393	2 trials compared acupuncture with wait list: both positive; 3 trials compared acupuncture to placebo: 2 positive; 2 trials compared acupuncture to physical therapy: both negative	Acupuncture may play a role in the treatment of osteoarthritis of the knee; additional research is necessary
Acute dental pain	Ernst and Pittler (39)	1998	16	941	12 trials suggested that acupuncture is more effective than controls; 4 trials suggested the contrary	Acupuncture can alleviate dental pain
Neck pain	White and Ernst (40)	1999	14	724	7 positive and 7 negative; acupuncture was not superior to placebo in 4 of 5 trials	Insufficient evidence for claiming efficacy
Fibromyalgia	Berman et al. (41)	1999	3	149	All positive, including 1 high-quality study	Acupuncture may be effective; more high-quality trials needed
Headache (tension-type and cervicogenic)	Vernon et al. (42)	1999	8	264	Placebo trials: 2 positive and 4 negative; results of other trials were contradictory	Too few trials, and contradictory evidence precludes conclusions
Headache	Melchart et al. (43)	1999	22	1042	15 migraine, 6 tension, and 1 mixed; contradictory results in 8 trials that compared acupuncture with other treatments; positive trend in 14 trials that compared acupuncture to placebo	Trend in favor of acupuncture, but evidence not fully convincing

* Positive = significant positive finding for acupuncture compared with control; negative = no significant finding for acupuncture compared with control; RCT = randomized, controlled trial; TENS = transcutaneous electrical nerve stimulation.
† Review and analysis contain some trials that were not randomized.

research. These reviews most often report that trials of acupuncture efficacy are equivocal or contradictory. Four exceptions are RCTs of acupuncture for emesis and dental pain, which have been overwhelmingly positive, and RCTs of various addictions and tinnitus, which have been predominantly negative. Multiple reviews of identical conditions (for example, asthma or low back pain) generally use overlapping studies and occasionally reach conflicting interpretations. Tables 1 and 2 summarize these studies. The tables are a comprehensive list of all English-language systematic reviews appearing in peer-reviewed journals retrieved from MEDLINE, PsycINFO, Acular, and AMED as well as a compilation of published bibliographies.

In 1997, a National Institutes of Health Consensus Development Panel on acupuncture reviewed the avail-

Table 2. **Systematic Reviews and Meta-Analyses of Randomized, Controlled Trials of Acupuncture for Conditions Other Than Pain***

Condition	Study (Reference)	Year	RCTs, *n*	Patients, *n*	Findings	Conclusions
Asthma	Kleijnen et al. (44)	1991	13†		8 positive and 5 negative; 3 of the positive and 5 of the negative trials were of high quality	Claims of effectiveness not based on well-performed trials
Pulmonary disease	Jobst (45)	1995	16†	2937	10 positive; when "real" acupuncture was redefined retrospectively, results for acupuncture were positive in 14	Acupuncture is a safe and potentially effective treatment for bronchial asthma and COPD
Asthma	Linde et al. (46)	1996	15	307	All placebo-controlled: 7 positive and 6 negative; 2 unclear	Insufficient data to draw reliable conclusions
Chronic asthma	Linde et al. (47)	2000	7	174	Trial quality varied and results inconsistent	Insufficient evidence to make recommendations
Addiction	ter Riet et al. (48)	1990	13	—	Smoking: 11 positive and 1 negative; Alcohol: 1 positive	Claims of efficacy are not supported by sound trials
Weight reduction	Ernst (49)	1997	4	270	2 positive and 2 negative	Evidence contradictory and claims of efficacy not based on trial outcomes
Smoking cessation	Law and Tang (50)	1995	8	2759	Compared with control, 3% (95% CI, −1% to 6%) more of the patients treated with acupuncture stopped smoking	Acupuncture has little or no effect
Smoking cessation	White et al. (51)	1999	14	3486	Odds ratio, 1.20 (CI, 0.98% to 1.48%)	Acupuncture not better than placebo
Stroke	Ernst and White (52)	1996	5	425	All positive; none compared acupuncture with placebo	Evidence encouraging but not compelling
Stroke	Park et al. (53)	2001	9	538	6 positive and 3 negative; the best trial was negative	No compelling evidence for the effectiveness of acupuncture
Dentistry (mainly TMJ disorder)	Rosted (54)	1998	15		11 positive and 4 negative; most studies had methodologic problems	Acupuncture seems effective for TMJ disorders and facial pain; questions remain concerning use as an analgesic
TMJ disorder	Ernst and White (55)	1999	3	205	All positive; none compared acupuncture with placebo	Studies need confirmation with more rigorous methods
Emesis	Vickers (56)	1996	33†	3123	27 of 29 performed with no anesthesia were positive; in a second analysis that was restricted to 12 high-quality trials, 11 (almost 2000 patients) were positive	Acupuncture point P6 seems to be an effective antiemetic for cancer chemotherapy, pregnancy, and surgery
Emesis	Harris (57)	1997	12	904	Restricted to acupressure trials; acupressure more effective than placebo for nausea during pregnancy, after surgery, and for cancer chemotherapy	Acupressure can be used as an antiemetic
Nausea and vomiting of pregnancy	Murphy (58)	1998	7	686	6 positive and 1 negative; all were acupressure trials	Acupressure benefits many women, but evidence is equivocal
Postoperative nausea and vomiting	Lee and Done (59)	1999	19	1569	Pooled RR similar to antiemetics in preventing early vomiting (RR, 0.89) and late vomiting (RR, 0.80); better than placebo for early nausea (RR, 0.34) and early vomiting (RR, 0.47)	Acupuncture is similar to antiemetics in preventing early vomiting and late vomiting in adults; may be an alternative to receiving no treatment or first-line antiemetics; no benefit in children
Nausea and vomiting of pregnancy	Jewell and Young (60)	2001	4	—	3 positive and 1 negative; the negative trial was the most rigorous	Clear evidence for beneficial effects but results remain equivocal
Tinnitus	Park and White (61)	2000	6	185	2 unblinded positive trials and 4 blinded negative trials	Acupuncture not demonstrated to be efficacious

* Positive = significant positive finding for acupuncture compared with control; negative = no significant finding for acupuncture compared with control. COPD = chronic obstructive pulmonary disease; RCT = randomized, controlled trial; RR = relative risk; TMJ = temporomandibular joint.
† Review and analysis contain some trials that were not randomized.

able evidence from RCTs and reached the following conclusions:

> There is clear evidence that needle acupuncture is efficacious for adult postoperative and chemotherapy nausea and vomiting and probably for nausea of pregnancy.
>
> Much of the research focuses on various pain problems. There is evidence of efficacy for postoperative dental pain. There are reasonable studies (although sometimes only single studies) showing relief of pain with acupuncture on diverse pain conditions. . . . However, there are also studies that do not find efficacy for acupuncture in pain. . . .
>
> Although many other conditions have received some

> attention. . . , the quality or quantity of the research evidence is not sufficient to provide firm evidence of efficacy at this time (62).

The research published after 1997 does not provide significant data to modify or contradict this statement.

Methodologic Issues in RCTs of Acupuncture

With a few important exceptions, RCTs designed to test the efficacy of acupuncture seem to produce contradictory outcomes that resemble random events. Several other treatments that do not involve drugs (especially those for pain, for example, TENS [transcutaneous electrical nerve stimulation], therapeutic ultrasonography, and epidural corticosteroids for sciatica) have similarly confusing results (63). Most systematic reviews of acupuncture have called for higher-quality trials to resolve such inconclusive evidence.

Some of the problems encountered with acupuncture RCTs are shared by RCTs in many domains: insufficient sample size, testing in poorly defined illnesses with imprecise outcomes, vague enrollment criteria leading to heterogeneous study groups, high dropout rates, and inadequate follow-up.

Some of the problems are specifically related to the difficulty in performing RCTs with acupuncture. In RCTs, acupuncturists may have positive expectancy, which is likely to introduce significant bias (64). In many situations, blinding the acupuncturist to avoid such performance bias may be an insurmountable problem (65, 66). The quest for a matching sham control—one that is inert, identical in appearance and sensation, and without nonspecific physiologic effects (such as the release of neurotransmitters, which may affect pain thresholds)—is ongoing (67–70). An inordinately high placebo effect from acupuncture may complicate detection of any intervention–sham difference (71).

Lack of knowledge by researchers may aggravate the problems associated with evaluating the efficacy of acupuncture. For example, the supposedly active acupuncture arm of some RCTs may actually have been more suitable as a dummy treatment (72). How to authentically apply acupuncture-flexible diagnostic categories and process-oriented outcomes within the rigid protocols often necessary for RCTs continues to provoke debate in the research community (73). The heterogeneity of acupuncture techniques themselves challenges researchers: Which category of acupuncture should be tested, and, within each category, how much variability can be allowed (74)? For example, in the asthma RCTs, only two trials by the same author used the same acupuncture points (75). It is probably not an accident that the most unequivocal evidence for acupuncture is based on a series of 30 trials that used a fixed, "druglike," well-defined research model of a single acupuncture point for a particular symptom (emesis), even though this method has little relevance for the daily practice of acupuncture (76).

Basic-Science Evidence

Numerous surveys show that, of all the complementary medical systems, acupuncture enjoys the most credibility in the medical community (77). The RCT research is probably not the main basis for this positive opinion. A more likely reason is the existence of a substantial body of data showing that acupuncture in the laboratory has measurable and replicable physiologic effects that can begin to offer plausible mechanisms for the presumed actions. Extensive research has shown that acupuncture analgesia may be initiated by stimulation, in the muscles, of high-threshold, small-diameter nerves. These nerves are able to send messages to the spinal cord and then activate the spinal cord, brain stem (periaqueductal gray area), and hypothalamic (arcuate) neurons, which, in turn, trigger endogenous opioid mechanisms. These responses include changes in plasma or corticospinal fluid levels of endogenous opioids (for example, endorphins and enkephalins) or stress-related hormones (for example, adrenocorticotropic hormone) (78).

In one study, the effects of acupuncture in one rabbit could be transferred to another rabbit by cerebrospinal fluid transfusions (79). Although questions remain (80, 81), other studies have shown that acupuncture analgesia could be reversed with naloxone (an endorphin antagonist) in a dose-dependent manner (78, 82). Acupuncture may inhibit early-phase vascular permeability, impair leukocyte adherence to vascular endothelium, and suppress exudative reaction to a degree equivalent to that of orally administered aspirin and indomethacin (83). Evidence also supports the possibility that one mechanism of acupuncture may be a form of stimulation for the gene expression of neuropeptides (84, 85).

Functional magnetic resonance imaging is also be-

Table 3. **Reported Adverse Events Related to Acupuncture Treatment from November 1992 through October 1997***

Reported Adverse Event	Patients, *n*
Forgotten needles	16
Dizziness, discomfort, or perspiration (transient hypotension)	13
Burn injury (caused by thermotherapy)	7
Ecchymosis with pain	6
Ecchymosis without pain	5
Malaise	5
Minor hemorrhage	3
Aggravation of symptoms	3
Itching or redness (suspected contact dermatitis)	3
Pain in the puncture region	2
Fall from bed	1

* Total number of acupuncture treatments was 55 291. Reprinted with permission from Yamashita et al. (105).

ginning to demonstrate that acupuncture has regionally specific, quantifiable effects on relevant structures of the human brain. One study found that a specific acupuncture point, traditionally related to vision, activated an occipital lobe region that was the same area activated by stimulation of the eye using direct light. The point was located on the lateral aspect of the foot; stimulation of nearby sham points did not result in similar activation (86). Other studies show that specific acupuncture points, but not controls, activate structures of descending antinociceptive pathways and deactivate multiple limbic areas that participate in pain processing (87, 88). These functional magnetic resonance imaging studies follow earlier efforts showing that electro-acupuncture results in significantly increased concentrations in the rat brain (specifically, the occipital cortex and hippocampus) of neuropeptide Y, neurokinin A, and substance P (89).

Adverse Events Associated with Acupuncture

Numerous retrospective clinical reports and at least five published systematic reviews of adverse events associated with acupuncture show that, in rare circumstances, acupuncture can produce the complications associated with any type of needle use (90–96). Negative outcomes include transmission of infectious disease, pneumothorax and other problems associated with organ punctures, cardiac tamponade, and broken needles with remnants migrating to other locations (including the spine). Five incidents may have resulted in death (97), although some researchers refute this possibility (98). Adverse events usually occur when acupuncturists have inadequate training (99).

The reports of adverse events described above are based mainly on retrospective reports. More recently, prospective, systematic surveillances of acupuncture adverse events (which provide a denominator for relative rates) have been performed and indicate that even routine irritating reactions from needles are rare (100–104). For example, one study that followed more than 55 000 treatments at an acupuncture training facility in Japan found 11 adverse effects associated with acupuncture treatment (Table 3) (105). The combined data from prospective and retrospective data indicate that "acupuncture is a very safe intervention in the hands of a competent practitioner" (106).

THE PROVISION OF ACUPUNCTURE CARE IN THE UNITED STATES

In 1976, California became the first state to license acupuncture as an independent health care profession. Since then, 40 states and the District of Columbia have adopted similar laws. Most states (27) allow herbal medicine within the scope of acupuncture practice; only a few states (10) require the supervision of a physician for the almost 11 000 practicing nonphysician acupuncturists.

The number of acupuncturists is rapidly growing and is projected to double by 2005 and quadruple by 2015 (107). The typical education standard for an acupuncturist is between 2000 and 3000 hours of training in independently accredited master's degree 4-year schools. Although some states allow physicians to practice acupuncture without additional education, most states require between 200 and 300 hours of special training. There are approximately 3000 acupuncturists with medical degrees practicing in the United States. Physician and nonphysician acupuncturists independently maintain that their provision of care is superior (108).

In the West, most patients of acupuncture practitioners present with pain resulting from numerous conditions, including musculoskeletal disorders, headaches or migraines, and neuralgia or neuropathy (109–111). Gastroenterologic, urologic, and gynecologic diseases are also fairly represented. Approximately 70% of acupuncturists practice alone or in acupuncture groups; 30% work in multidisciplinary settings, usually in association with other alternative providers. Typically, acupuncture care involves a series of biweekly or weekly treatments; a regimen of a dozen treatments is not unusual. Including examination, treatment, and discussion, acupuncture visits are characteristically long, usually exceeding 1 hour (Cooper RA, McKee HJ. Education of health professionals in complementary/alternative medicine. Presented at the Josiah Macy Jr. Foundation Conference, Phoenix, Arizona, 2–5 November 2000). In the West, reports indicate that 50% (112) to 80% (113) of acupuncturists also prescribe herbal medicine.

CONCLUSION

In a short time, acupuncture has been transported to the West and become a visible component of the health delivery system. Its traditional conceptual framework is radically distinct from biomedicine. Research on acupuncture has allowed a consensus to emerge that this therapy may have efficacy, regardless of the "prescientific" perspective of its underlying conceptual framework. As an independent profession, acupuncture and East Asian medicine are growing exponentially.

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Stress in Medical Residency: Status Quo after a Decade of Reform?

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Background: **Although curricular reforms have attempted to address sources of stress in medical residency, no recent studies have examined the financial or emotional situations of current medicine residents.**

Objective: **To question medicine residents about financial status, educational debt, moonlighting, and psychological issues.**

Design: **Survey distributed in a nonrandomized fashion to medicine residents.**

Setting: **All 415 U.S. medicine residency programs.**

Results: **According to the questionnaire responses submitted by the 4128 (18%) participating residents, a substantial number of residents had financial and emotional distress that could have interfered with training. The reported educational debt was at least $50 000 for 1657 (42%) of the respondents and at least $100 000 for 737 (19%). The monthly disposable income was $100 or less for 1620 (43%) of the residents, and 637 residents (16%) could not afford safe housing. Among respondents in their 2nd through 5th year of postgraduate training, 2187 (52%) had insufficient funds to purchase books and equipment, and 678 (29%) could not afford the required fees for the American Board of Internal Medicine certifying examination; 2659 (33%) worked as moonlighters, and this percentage increased progressively with increasing educational debt.**

Four or five depressive symptoms during residency were reported by 1461 (35%) residents. Eight hundred ninety-nine residents (23%) thought they had become less humanistic over the course of their residency training; 2347 (61%) reported becoming more cynical. Female residents were more likely than male residents to report increased cynicism and multiple depressive symptoms. Increased cynicism and depressive symptoms were associated with increasing educational debt.

Conclusions: **Despite recent curricular reforms, an alarming number of current medicine residents report depressive symptoms, increasing cynicism, and decreasing humanism, which were associated with increasing educational debt and a need to moonlight for financial survival. Ongoing curricular reform, legislative relief from early loan repayment, and salary increases may be necessary to address these problems.**

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See related article on pp 358-367 and editorial comment on pp 394-396.

During the 1970s and 1980s, medical educators attempted to examine the quality of the personal and professional lives of residents. Several small nonrandomized studies found a higher incidence of depression (1–4) and anger and hostility (5, 6) in residents than in the general population. These findings were partly attributed to chronic sleep deprivation and fatigue (7–11). In response, residency program directors suggested (12) and implemented procedures to identify, manage, and reduce resident stress and impairment. Although residents may still be overworked (13), duty hours are now carefully regulated, and program directors are required to regularly monitor resident stress (14). Currently, the American Board of Internal Medicine and others (15) emphasize the importance of fostering outstanding professional and humanistic characteristics in residents. Some researchers have suggested a link between long work hours and loss of professionalism among residents (13, 16).

New sources of stress to residents continue to emerge. These include increasing personal debt from medical school (17–20), unstable financial conditions in many academic medical centers, threats of residency closings (21), and decreased confidence in the availability of jobs upon completion of residency (22–24). Furthermore, an increasing effort is required to master a rapidly expanding scientific and clinical knowledge base. Patients are sicker and are discharged faster on inpatient services, and many residents continue to be overworked, despite regulations (25). Worse yet, the residents' role models and teachers often openly express discontent with the practice of medicine (26).

METHODS

To re-examine current residents' psychological and financial situations, the Resident Services Committee of the Association of Program Directors in Internal Medicine (APDIM) mailed a survey in May 1998 to all 415 internal medicine program directors, who were asked to distribute copies to each of their medicine residents (residents in categorical, preliminary, and combined tracks). Strict confidentiality was assured, and no specific names of residents or programs were included in the question-

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Table 1. **Comparison of Demographic Data of Responding Residents with 1997–1998 Figures for U.S. Internal Medicine Residents***

Characteristic	Residents Completing the Current Survey	U.S. Internal Medicine Residents†
	n (%)	
Sex		
Female	1794 (39.8)	8745 (37.5)
Male	2719 (60.2)	14 478 (62.5)
Year of residency training		
PGY 1	1444 (35.4)	8903 (38.2)
PGY 2	1283 (31.4)	7018 (30.1)
PGY 3	1237 (30.2)	6662 (28.6)
PGY 4	114 (2.8)	711 (3.1)
PGY 5	6 (0.15)	13 (0.06)

* PGY = postgraduate year.

† Data on U.S. internal medicine residents obtained from the Graduate Medical Education Database, 1997, American Medical Association, Chicago, Illinois. This cohort included residents in medicine-pediatrics and medicine-emergency medicine training programs.

naire. Residents were questioned about demographic data, moonlighting activities, and finances, including monthly disposable income, student loan debt, and credit card debt. They were also asked whether they had experienced any or all of five depressive symptoms and whether they felt that they had become more or less cynical and more or less humanistic during residency training. Data on all respondents were included in the analysis, with missing data noted.

RESULTS

Demographic Data and Response Rate

We received responses from 4128 (18%) of the medicine residents in the United States in 1998 (Table 1). The decision to maintain confidentiality made follow-up of nonrespondents impossible, and it is unknown how many residents received but did not complete the survey. In addition, the survey design precludes interpretation of these results as representative of all residents. Just as it is unlikely that we achieved a statistically accurate sampling of the resident population, it is also doubtful that all residents with serious personal difficulties responded. These factors prevent us from determining the true proportion of residents with financial or emotional distress.

Financial Data

Table 2 shows the financial data of responding residents. Among the 3961 residents who indicated their estimated educational debt, the average amount was $44 412 and the median was $25 000; 1657 residents (42% of responders) reported owing at least $50 000 in educational debt. The average estimated credit card debt was $3769; 1224 residents (31%) reported having at least $3000 in credit card debt, and 320 (8%) reported at least $15 000. From postgraduate year (PGY) 1 to PGY 4, the mean credit card debt increased from $3275 to $6194. One thousand six hundred twenty responding residents (43%) had a monthly disposable income—defined as income remaining after payment of required bills of food, rent, utilities, and debt—of $100 or less, including many with a negative monthly disposable income.

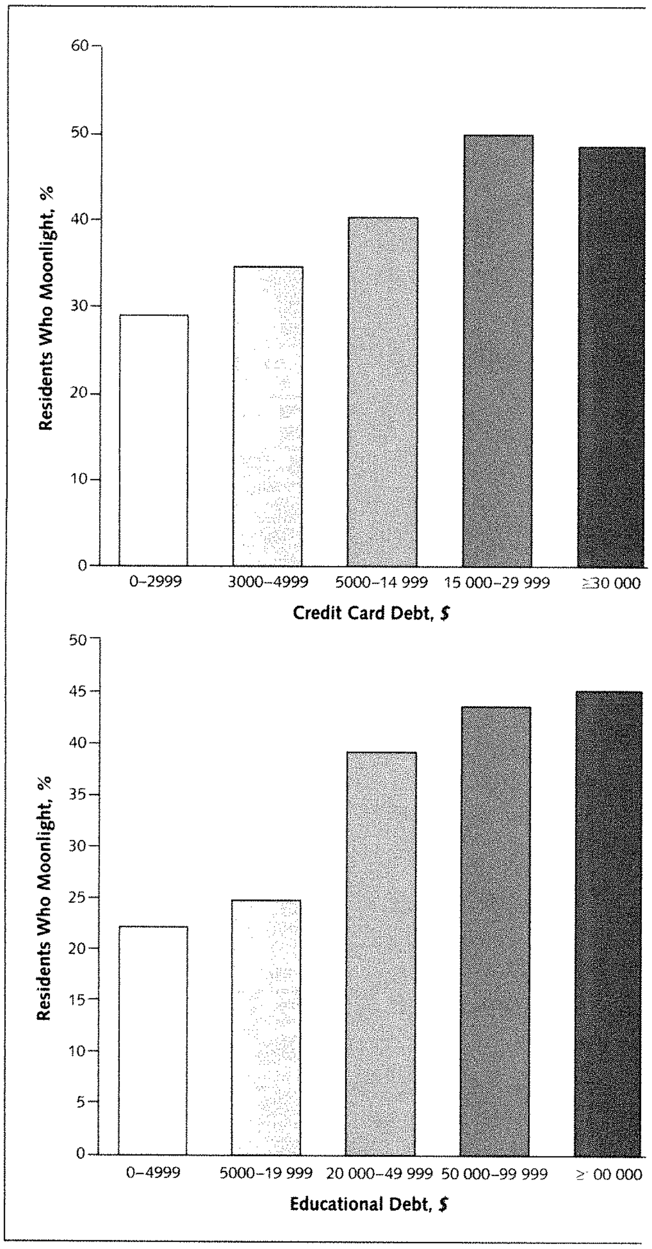
Two thousand one hundred eighty-seven residents (52%) reported having insufficient funds to purchase work items, such as books and equipment. Six hundred seventy-eight (30%) PGY-2 through PGY-5 residents could not afford the fee for the American Board of Internal Medicine certifying examination, and, most disturbingly, 637 responding residents (16%) could not afford safe and sufficient housing. Only 10%, however,

Table 2. **Financial Data on Responding Residents**

Estimated Educational Debt		Estimated Credit Card Debt		Monthly Disposable Income*	
Amount	Residents	Amount	Residents	Amount	Residents
$	*n (%)*	*$*	*n (%)*	*$*	*n (%)*
0–4999	1692 (42.7)	0–2999	2756 (69.2)	0–100	1620 (43.1)
5000–19 999	182 (4.6)	3000–4999	220 (5.5)	101–200	549 (14.6)
20 000–49 999	430 (10.9)	5000–14 999	234 (5.9)	201–500	1041 (27.7)
50 000–99 999	920 (23.2)	15 000–29 999	234 (5.9)	≥501	550 (14.6)
≥100 000	737 (18.6)	≥30 000	86 (2.2)		

* Monthly disposable income was defined as income left over after payment of required bills of food, rent, utilities, and debt.

Figure 1. **Relationship of credit card and educational debt to moonlighting.**



said that salary was a consideration in choosing a specialty.

Moonlighting

Of 2629 responding PGY-2 through PGY-5 residents, 857 (33%) had moonlighting jobs. Among the moonlighters, 167 (20%) worked 21 to 30 moonlighting hours per week, 101 (12%) worked 31 to 40 moonlighting hours per week, and 81 (9%) worked more than 40 moonlighting hours per week. Among those who completed the survey, moonlighting progressively increased with increasing educational and credit card debt (**Figure 1**). Fifty-four percent of moonlighting respondents had at least $50 000 in educational debt compared with 34% of nonmoonlighters. Similarly, 35% of moonlighters had at least $5000 of credit card debt compared with 22% of nonmoonlighters. Moonlighters were more likely to have sufficient money for books and equipment but were no more likely to be able to afford the board examination. Moonlighters and nonmoonlighters did not differ significantly in the amount of end-of-month disposable income ($292.60 vs. $294.36).

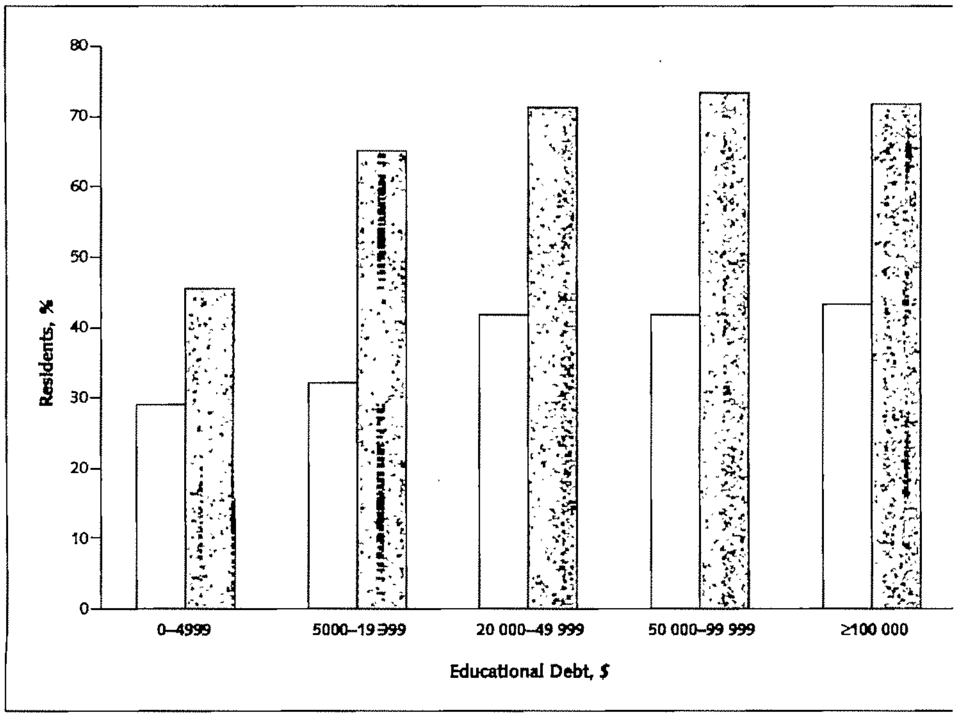
Depressive Symptoms, Cynicism, and Humanism

A substantial number of residents reported depressive symptoms since starting residency. Forty-nine percent had experienced appetite changes; 61%, mood swings; 52%, decreased recreational activities; 45%, depressed mood; and 74%, sleep disturbance. Four or five depressive symptoms were reported by 1461 residents (35% of respondents), and 991 (22%) reported all five symptoms. Seventeen percent reported a loss of a loved one or close friend during residency. Eight hundred ninety-nine responding residents (23%) reported becoming less humanistic during residency training, and 2347 (61%) reported becoming more cynical. Importantly, among survey respondents, increasing debt correlated with self-reports of increasing cynicism and multiple depressive symptoms (**Figure 2**).

Responses of Female Residents

Forty percent of responding female residents (n = 667) and 32% of responding male residents (n = 777) noted four or five depressive symptoms. Sixty-seven percent of responding female residents (n = 1033) reported increasing cynicism versus 56% of responding male residents (n = 1294). Eighty-five percent (n = 1342) of female respondents believed that residency increased the complications of pregnancy. Twenty-eight percent of responding female residents (n = 328) felt faculty pressure to delay pregnancy, and 52% (n = 533) said that peers were resentful about pregnancy and maternity leave.

Figure 2. **Relationship of educational debt to depressive symptoms and increased cynicism in physician residents.**



White bars = residents with four or five depressive symptoms; gray bars = residents with increased cynicism.

Residents with children less often reported feelings of depression than residents without children (41% vs. 47%). Similarly, residents with children less often reported increased cynicism (50% vs. 65%) and more often reported increased humanistic feelings (27% vs. 23%).

DISCUSSION

Our survey indicates that despite extensive efforts to reduce stress during residency, many medical residents had financial and emotional distress that could have interfered with training. Although our study is, to our knowledge, the largest to have examined these issues in this population, it is unlikely that the responses represent a statistically accurate sampling. However, even if we assume that only discontented, maladjusted, or financially distressed residents returned the survey, the absolute number of internal medicine residents reporting significant problems must serve as a serious alert to all concerned with our medical educational system and demands remediation.

In 1996, Reynolds (27) reported an average debt of $39 707 in internal medicine residents, which is similar to our figure of $44 412. The average debt in our study is lower than the 1997 mean medical student debt of $80 462 reported by the Association of American Medical Colleges (19, 28). A possible explanation for the reduced amount may be that residents with lower debt, such as those who graduated from publicly supported institutions, are overrepresented among our survey respondents (28). Furthermore, a disproportionately greater percentage of the residents working in internal medicine training programs are international medical graduates, most of whom have no educational debt (29). Although studies have shown that increasing debt only weakly affects specialty choice (30–32), very high debt (33, 34) may reduce the likelihood that a medical student will choose a career in primary care.

In our survey, residents with debt more often turned to moonlighting as an extra source of income. Moonlighting did not generate increased disposable income, and thus, the extra income from moonlighting was probably being used to pay for debt services and fixed monthly expenses. The rate of moonlighting among respondents is similar to rates in several previous nonrandomized studies (23% to 40%) (35–42). Moreover, similar to earlier studies, educational debt in our study correlated with increased moonlighting. Of great concern is that 349 (40.7%) moonlighting respondents worked more than 20 hours per week at their moonlighting jobs. The substantial time spent moonlighting, combined with an average 80-hour work week of most residents, could result in undue fatigue and potentially jeopardize resident education and patient care.

Other studies (27, 30) have noted that debt repayment markedly decreases satisfaction with personal lifestyle during residency by limiting time for leisure activities. Although we did not specifically ask about lifestyle, 43% of respondents had less than $100 of monthly disposable income, which is clearly insufficient to support substantial leisure activities. Undoubtedly, many residents must borrow money, perhaps from family members, to cover their most basic needs and to pay for unexpected expenses, additional professional costs, or personal entertainment.

Emotional distress in residents—especially depression—has been well documented (1–4, 6). After conducting structured psychiatric interviews, Valko and Clayton (1) concluded that 30% of the residents they interviewed had significant depression during internship. Using the Center for Epidemiologic Studies scale, Reuben (2) demonstrated that 28.7% of the medical interns tested were depressed, and Ford (6) found that 33% of interns rated themselves as depressed. Our finding that approximately 35% of respondents noted four of five depressive symptoms is similar, and is higher than the estimates for the adult U.S. population, which has a lifetime risk of 7% to 25% and a point prevalence of approximately 5% (43, 44).

Despite the efforts of most training programs to improve professionalism in their graduates, more than half of the responding residents reported increasing cynicism, and 25% reported decreasing humanism during residency. Increasing cynicism has also been seen in medical students (45) and may be related to increasing anger during residency (5).

Our study also suggests that the unique mental health needs of many female medicine residents are not being met. More female respondents reported depressive symptoms and increased cynicism than their male counterparts. In addition, large numbers of female residents expressed concerns about the possibility of future pregnancy, an added stress from faculty and peers. The increased stress of pregnancy during residency, concerns about the pregnancy experience, and increased hostility from male peers have been well documented (49–57). Female residents' concern about increased medical complications of pregnancy during residency has been noted previously, despite evidence that, except for increased preterm labor, the outcomes of pregnancy are not greatly affected by residency training (58–64). However, one recent study from Israel (65) showed an increased incidence of stillbirths, and a 1988 study (66) showed a trend toward increased pregnancy-induced hypertension. Thus, although the preponderance of evidence is reassuring, some evidence supports the concern of female residents in our survey about the increased medical complications of pregnancy during residency training.

Our finding that parenthood reduced the stress of residency in some of the respondents is intriguing. How parenthood may blunt the negative effect of financial stress and may confer greater humanism and less cynicism needs further exploration. Perhaps being a young parent engenders hope in the future and a more altruistic view of life, or the family unit may act as a stabilizing force in the resident's life.

RECOMMENDATIONS

Although the limitations of our study are clear, we have identified a significant number of residents with alarming financial and psychological distress. The large number of residents in whom increasing debt burden correlated with self-reports of depressive symptoms, increasing cynicism, and increasing need for moonlighting for financial survival is of great concern. Leaders in academic medicine must develop solutions to the significant negative impact of debt. Relief—in the form of tuition subsidies for medical education, increases in residents' salaries, full loan deferral of principal and interest without interest accrual during residency training, and improved financial advice for residents—are all pieces of a solution to this major problem. Of note, efforts to limit moonlighting through regulation should be undertaken with caution in the absence of concomitant measures to alleviate the financial distress of residents. Finally, program directors, medicine department chairs, and senior medical education leaders must become aware of the additional stress in the lives of at least some of their female residents and develop systems in their programs for detection and prompt intervention.

Successful training of well-educated, humanistic physicians is a priority, and current stresses may thwart the accomplishment of that goal in some residents. We hope that this perspective paper will stimulate medical educators to further study the extent and causes of resident stress in both male and female residents in a randomized fashion. More important, our own results should mobilize the medical education community to respond immediately and effectively to the unmet needs expressed by many of the trainees under our care.

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Who Is Sicker: Patients—or Residents? Residents' Distress and the Care of Patients

Is burnout in residents a malignant disease? Do exhaustion, cynicism, and ineffectiveness start small, then grow, spread, and harm? Do they extend to students, other residents, patients, career, family? If so, what is the pathogenesis? What is the treatment? Can we prevent, cure, or heal this? Should anyone care?

Starting with the last question, there is growing evidence that, despite generations of denial, physicians' feelings matter. Grol and colleagues (1) have shown that frustrations, tensions, and annoyance with time pressures are linked to giving patients short shrift: Physicians may write a plethora of prescriptions yet give a paucity of time to listening and explaining (1). Conversely, physician satisfaction is associated with patient adherence to medical regimens (2) and patient satisfaction (3, 4). It is obvious that patients should care if residents—and older physicians, nurses, and other health professionals, for that matter—are depleted and discouraged. Physicians and their families should also care because professional experiences and attitudes can affect home life (5). Policymakers should care because the health of our society depends in part on the health and effectiveness of health professionals. Medical educators should worry: The problem is happening on their watch.

Maslach and others (5, 6) have demonstrated that burnout in many walks of life happens because of work. Workers are not the culprits; rather, work load, practices, conflicts, and environment are. Tensions may rise for some physicians (and others) as work pressures combine with home pressures, such as having child-care responsibilities (7) or having a spouse who frequently works overtime (8). The bulk of discouragement and alienation, however, stems from work, as shown by studies elsewhere in the health care arena: Excessive work demands in hospital nursing units have been linked to nurses' distress (9), a high mortality rate in intensive care units (10), and patient dissatisfaction (11).

These negative consequences of work burdens are expensive. If a physician gives up his or her clinical practice, for example, replacement costs are about $250 000 (12). Dollars do not begin to compensate for the adverse effects on physicians' physical or emotional health or on the family and friends. Patients' well-being is at stake, of course. The ripple effects of debility and growing dislike of patients and oneself—hallmarks of burnout—multiply and extend throughout society.

If burnout in residents and other health professionals has been a silent but costly malignancy, Shanafelt and colleagues (13) have made a good start at exposing this issue. They describe an underappreciated area and stimulate important questions. The investigators studied the association between residents' feelings of being depleted, negative, and inadequate and their opinions about the quality of care they gave patients. Researchers achieved a good response rate from internal medicine residents at an exemplary U.S. program, who answered an extensive questionnaire that examined feelings, habits, attitudes, personal remedies for distress, and patient care practices.

Their results should make any patient or physician snap to attention: 76% of 115 residents met criteria for burnout. Of those with burnout, more than half judged that they had rendered suboptimal care at least monthly compared with 21% of residents who were not at a low ebb.

How convincing are the report's conclusions? The authors themselves note limitations of the study, such as timing (February is a low morale month), distortions of self-reporting, unmeasured confounders, and the inability of a cross-sectional design to determine cause and effect. Other residents have been studied with similar findings (14), however, and other links have been made between health care professional distress and patient satisfaction and outcome (1–3, 9–11). One might question the validity of some of the survey measures introduced by the authors (but the survey questions do reflect the authors' vivid experiences). The scale for "feeling rushed" ranged from "never" to "weekly"; by omitting the response options of "daily" and "hourly," the authors may have missed the opportunity to capture fully the desperation of a hectic rotation. Also, "feeling rushed" is not necessarily bad, because this could provide an incentive to act. Moreover, the definitions of "suboptimal care" could be revised to permit more precise measurement. Finally, the report does not address the effects of residents' distress on friends and family.

Overall, however, their conclusions are reasonable, sobering, and galvanizing.

This study has both narrow and broad implications. For training-program leaders, several questions arise. Does the decreasing response rate from 90% among 1st-year residents to 62% in 3rd-year residents indicate increased exhaustion or apathy as training proceeds? Does the nearly double incidence of burnout in residents who took a break between college and medical school reflect age, commitment, or competing responsibilities or interests? Does the apparent correlation between burnout and depression mean that we should look more assiduously for depression in house officers? Did Shanafelt and colleagues document only a "February phenomenon" or a downward spiral that lasts for years? When 40% or more of the entire group identifies inadequate sleep, frequent shifts of longer than 24 hours, and inadequate leisure as major stressors, shouldn't work loads be changed? When we learn that talking with family members, significant others, and colleagues is a major coping strategy for 75% of the surveyed residents, shouldn't we provide the time and opportunity for such interactions? When 97% cite "at least 4 days off per month" as a residency program feature important for managing stress, what can be done to ensure more than 4 days off per month? Whether for short-term or long-term benefit, we can see that curriculum and scheduling are fruitful areas for intervention and study. Establishing and evaluating ways to maintain relationships in and outside the training program clearly are as essential as detecting and treating residents' emotional and physical problems.

What about the big picture? Patients and the public cannot imagine the outgrowths of physician burnout. We, on the other hand, have little difficulty doing so; we have seen it happen. An early sign may be as innocent as, "My calendar is really a wish list." Then, "I'm miserable." Then, "I think they are trying to kill me." Then comes disability, early retirement, or worse. The results are a sad, premature loss of knowledge and wisdom for patients and the public accompanied by profound distress for physicians and their loved ones.

Recognizing this sequence is different from proving and preventing it. We urgently need to study the relationships among physicians' states of mind, body, and spirit; their professional and personal performance; and outcomes of care. The pioneering work of investigators such as Shanafelt and colleagues points toward connections among these areas. We need more research and funding to amplify and confirm them. Even now, we need humane teaching, adequate staffing, and programs that help physicians and other health professionals to stay in top condition. Possibilities for research in this realm are plentiful, as are suggested interventions (14–20).

Long before research results are known, however, we know from experience and instinct that the core, the *cor*, of our profession must be healthy so that we, ourselves, and our patients, families, and communities are healthy. We must pay attention now to the information that we have already, and we must act. We can work on our own behaviors; we should gather like-minded colleagues and work on our institutions and systems.

The paper by Shanafelt and colleagues is about distress and care. It is also about values. Values are a source of our passions, motivation, and energy. Values fuel our purpose and, when we are aware of them, help direct our decisions. The paper is also about relationships, attitudes, learning, and time. When they are in sufficient supply, these assets are our allies. However, because they are so exhausted, I say to residents and established physicians, "Rise up." Yes, *rise up*!

It is simply unacceptable for new—or more established—physicians and other health professionals to be in such great pain. It is improper for us to sacrifice our own health, family, and community in order to care for others. Part of our calling is to relieve suffering. We cannot relieve the suffering of others if we, ourselves, are suffering. Poets and musicians may function better when they are melancholy, but physicians do not.

We need to take care of ourselves. That is not selfish. It is smart, and no one else will do it for us. We also need to take care of our residents. Who else will? What message are we giving when we ignore them? We need to show residents and each other that they and we matter. A former resident, now a friend and mentor, recently told me

> You were the only person who paid any attention to me in the entire training program. One day, when we were on rounds, and I was coughing a lot, you said to me, "Better get that checked out . . . *today*." I was stunned—an attending was telling me to get checked *today*? Well, it's a good thing that I took your advice: I was having my first asthma attack.

We need to reflect, plan, arrange, choose, and demand a *whole* life. This goes beyond choosing to be "excellent" in our profession. It extends to the rest of our lives—to our souls and to our loved ones and society. We need to speak up—to *participate*. We need to *learn* ways to navigate the treacherous intersections of professional and personal lives because competing demands of work and home can break our hearts just as patients' tragedies can.

Making these changes takes work and time, but we should never lack sufficient time to savor being a person as well as a physician. Physicians (or other health professionals) can teach each other about these central matters. We can present renewing grand rounds and seminars. We can convene series of conversations about values, success, power, duty, barriers and boosters to change, practical tips to leading a complicated life, and so forth. The next steps entail going from presentations and conversations to reflection to action.

Goethe said, "Thinking is easy. Acting is difficult." We have an important cause, however. We want to prevent and cure this malign condition called burnout, which leads to valuable, competent people feeling angry and weary. We need to recapture our health, effectiveness, creativity, commitment, and even joy. It can be done. I have seen it happen.

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Disclosure: Dr. Clever receives compensation as president of Renew!, a nonprofit organization dedicated to returning health to health professionals.

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Heeding the Plea To Deal with Resident Stress

In the old days—let's say 30 or 40 years ago—concerns about the well-being of medical residents centered on such issues as adequate parking spaces, midnight snacks, and off-hours access to the library. The pace of life was a lot slower, and the stresses were a lot more manageable. This is not to say that a resident's life was "a piece of cake" back then. We all worked long hours, routinely spent every other night and every other weekend in the hospital, had precious little time for "leisure activities," were paid next to nothing, and worried a lot about money. But, as I recall, we were a pretty happy lot. The feeling of camaraderie was intense, the light at the end of the tunnel was clearly visible, and we were totally caught up in the excitement of caring for our own patients and learning how to be good physicians. On balance, the hardships were more than offset by the satisfactions.

I confess that my recollections of residency may have acquired the gloss of rosy retrospection, but I'm quite sure that the psychological state of my contemporaries was much less troubling than appears to be the case for residents today. The stresses, both professional and personal, that residents now experience do seem to be much more intense than in the past: Patients are sicker, hospital stays are shorter, and attendings are more hassled; many more residents are married, many have children, and a great many more are women. All of these contemporary realities are potential sources of added stress.

To make matters worse, the sources of offsetting satisfaction (dare I say joy) appear to be drying up. There are fewer opportunities to establish relationships with patients, not to mention with peers and faculty; there are fewer occasions to experience the sheer pleasure of learning; and, in the unsettled new world of medicine, there are fewer thrills to be had from contemplating one's future gratification as a practitioner.

So, there is ample reason to be concerned about the health and welfare of today's medical residents. Indeed, data such as those presented by Collier and colleagues (1) in this issue reconfirm what we have known for some time: *The burdens that residents labor under are extracting an unacceptable toll on their well-being.* A higher incidence of depressive symptoms and a mounting titer of cynicism were the principal findings in the report. The authors concede that the relatively low response rate to their survey and the absence of follow-up information limit the utility of their study. However, they contend quite rightly that the de minimus interpretation of their findings is troubling enough to warrant careful attention. What is especially noteworthy from their observations is the effect on the level of resident stress attributed to the amount of debt acquired during the course of earning the doctor of medicine degree.

The level of indebtedness reported by the respondents to the authors' survey is alarming enough, but it is in fact far less than that reported by recent graduates of U.S. medical schools. Among those in the class of 2001 with debt, the average educational debt reported on the Association of American Medical Colleges' (AAMC's) Graduation Questionnaire (>90% response rate) was just shy of $100 000; only 17% of graduates reported having no outstanding loans (2). Perhaps the lower figure for indebtedness among the authors' respondents, as they suggest, reflects the relatively large fraction of internal medicine residents who are graduates of foreign medical schools and whose education generally requires far less personal investment.

It is certainly not hard to imagine how the burden of repaying a large debt can weigh heavily on a resident's mind and adversely affect both mood and behavior. Bouts of depression and excessive moonlighting, both suggestively correlated with the amount of debt, are not surprising as consequences. Add the worry of repaying one's debt to all the other well-known stresses endemic in the learning environment of graduate medical education today—too many hours on call, too many patients, too many mindless chores, too little teaching, too little sleep—and it is little wonder that probing questionnaires detect a growing cynicism among our residents.

The authors conclude their paper with a heartfelt plea for "the medical education community to respond immediately and effectively to the unmet needs expressed by many of the trainees under our care." In my view, heeding this plea is absolutely essential if we are to preserve the integrity of internal medicine, indeed of all of medicine. Continuing to ignore the glaring symptoms of distress among our acolytes is to abandon our solemn obligation as stewards of a noble profession.

So, what's our response to be? With respect to our residents' learning environment, we must recommit ourselves to "Honoring the E in GME." That was the title of my president's address at the 1998 AAMC Annual Meeting, in which I called for a significant enrichment of the educational content of residency programs; a strengthening of the institutional authority over individual graduate medical education (GME) programs; a limitation of service requirements to those necessary to meet educational objectives; and a much increased emphasis on inculcating professional values, especially by attending to the "hidden curriculum" and by treating our residents as true colleagues rather than as minions (3).

There are some hopeful signs on this score. For its part, the Accreditation Council for Graduate Medical Education is redoubling its efforts to enforce existing standards governing resident duty hours and institutional oversight of sponsored programs. The AAMC is also increasing its efforts to assist the GME leadership of our teaching hospitals and medical schools in improving the learning environment for residents.

With respect to the ever-increasing debt burden borne by medical school graduates, however, the signs appear less hopeful. First, there is little prospect that the costs of medical education, including the costs of living while in school, will decrease anytime soon. Given the unprecedented financial pressures facing medical schools and teaching hospitals, little prospect exists, as well, for more scholarship aid for medical students to minimize the need for borrowing or for significantly higher stipends for residents to help with loan repayment.

There also is little prospect that Congress, which views future physicians as economically privileged, will ease the financial pressure on residents by permitting deferment of interest payments on federally guaranteed loans. (Such loans account for about 36% of the outstanding debt hanging over residents' heads.) Likewise, there is little prospect that loan forgiveness programs, such as those sponsored by the National Health Service Corps, will be expanded. Despite intense lobbying on its behalf by the AAMC and others and despite its unquestioned success in using debt relief to recruit physicians to underserved areas, the National Health Service Corps continues to receive lackluster support from Congress.

Given these realities, the best hope in the short run for easing our residents' worry about how to repay their loans is to provide them with sophisticated advice about debt management. Fortunately, this source of solace is now widely available, albeit not yet widely known. In recognition that debt levels are destined to continue escalating for the foreseeable future, the AAMC has mounted an aggressive program to provide residents with the information and tools they need to minimize the stress engendered by the fear of defaulting on their loans. Information on this program, called the AAMC Educational Debt Management Services for Residents, can be accessed at www.aamc.org/debtmanagement.

Stress in medical residency has many root causes. Some are more amenable to relief than others. As medical educators, we can do much to alleviate the stress attributed to a harsh and demeaning learning environment. Doing so will help offset the less tractable stress from dealing with debt. It is also the right thing to do.

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POSITION PAPER

Physician–Industry Relations. Part 1: Individual Physicians

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This is part 1 of a 2-part paper on ethics and physician–industry relationships. Part 1 offers advice to individual physicians; part 2 gives recommendations to medical education providers and medical professional societies.

Physicians and industry have a shared interest in advancing medical knowledge. Nonetheless, the primary ethic of the physician is to promote the patient's best interests, while the primary ethic of industry is to promote profitability. Although partnerships between physicians and industry can result in impressive medical advances, they also create opportunities for bias and can result in unfavorable public perceptions.

Many physicians and physicians-in-training think they are impervious to commercial influence. However, recent studies show that accepting industry hospitality and gifts, even drug samples, can compromise judgment about medical information and subsequent decisions about patient care. It is up to the physician to judge whether a gift is acceptable. A very general guideline is that it is ethical to accept modest gifts that advance medical practice. It is clearly unethical to accept gifts or services that obligate the physician to reciprocate.

Conflicts of interest can arise from other financial ties between physicians and industry, whether to outside companies or self-owned businesses. Such ties include honorariums for speaking or writing about a company's product, payment for participating in clinic-based research, and referrals to medical resources. All of these relationships have the potential to influence a physician's attitudes and practices. This paper explores the ethical quandaries involved and offers guidelines for ethical business relationships.

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See related article on pp 403-406.

In 1990, the American College of Physicians published a position statement titled "Physicians and the Pharmaceutical Industry" to address ethical issues in relationships between industry and the medical profession (1). The statement, which was prompted in large part by evidence of the drug industry's influence on physician behavior and concern for professional integrity and patient care, examined potential conflicts of interest in relationships with industry and provided ethical advice in certain areas. Since the statement was originally released, evidence of industry's influence on medical practice, research, and education has continued to emerge, and physician–industry relationships have multiplied. Once again, the American College of Physicians–American Society of Internal Medicine reminds physicians and industry to be vigilant about potential conflicts and ethical problems. The College recognizes that while there are no easy answers to many ethical questions, guidance in certain areas can be useful.

This is part 1 of a 2-part paper on ethics and physician–industry relationships. In part 1, the College offers recommendations to individual physicians, mainly clinicians and clinician-researchers, regarding acceptance of gifts and other financial relationships with industry. Part 2 addresses medical education providers and medical professional societies that accept corporate funding for organizational projects or membership events, such as meetings and symposiums (see pp 403-406).

Despite the introduction in the early 1990s of ethical standards for physicians regarding physician–industry relationships, concerns persist and evidence accumulates that commercial rewards can unduly affect clinical judgment (2–9). Industry allocates substantial resources to promote its products to physicians. In 1999, the pharmaceutical industry spent nearly $8.0 billion (U.S.) to send sales representatives to physician offices and to exhibit products at medical conferences and events (10). Such costly corporate overtures raise questions about undue influence and could undermine genuine educational efforts.

In addition to the pharmaceutical industry, physicians are increasingly courted by newly emerging indus-

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* This paper was written by Susan L. Coyle, PhD, and was developed by the American College of Physicians–American Society of Internal Medicine (ACP–ASIM) Ethics and Human Rights Committee. Members of the ACP–ASIM Ethics and Human Rights Committee were William E. Golden, MD (*Chair*); David W. Potts, MD (*Vice Chair*); Harmon H. Davis II, MD; David A. Fleming, MD; Susan Dorr Goold, MD; Vincent E. Herrin, MD; Jay A. Jacobson, MD; Risa Lavizzo-Mourey, MD, MBA (*Past Chair*); Joanne Lynn, MD; and Daniel P. Sulmasy, OFM, MD, PhD. Lois Snyder, JD, Director of ACP–ASIM's Center for Ethics and Professionalism, provided principal staff support. This paper was approved by the ACP–ASIM Board of Regents on 15 July 2001.

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tries (biotechnology, pharmacogenetics, e-commerce), and potential conflicts of interest, whether real or perceived, are pervasive. Physicians meet industry representatives at the office and at professional meetings, collaborate in community-based research, and develop or invest in health-related industries. In all of these spheres, partnered activities often offer important opportunities to advance medical knowledge and patient care, but they also create an opportunity for the introduction of bias.

This paper offers two positions to help guide individual physicians in making ethical decisions about interacting with industry. The positions are based on the profession's fundamental principles of responsibility, that is, acting in a patient's best interests (beneficence), protecting the patient from harm (nonmaleficence), having respect for the patient and fostering informed choice (autonomy), and promoting equity in health care (justice). To uphold these principles, the primary purpose of entering relationships with industry should be the enhancement of patient care and medical knowledge. While the ethics of medicine and the ethics of business sometimes diverge, both are legitimate, and a thoughtful collaboration of physicians and industry can result in the best of patient care.

POSITION 1. INDUSTRY GIFTS, HOSPITALITY, SERVICES, AND SUBSIDIES

The acceptance of individual gifts, hospitality, trips, and subsidies of all types from industry by an individual physician is strongly discouraged. Physicians should not accept gifts, hospitality, services, and subsidies from industry if acceptance might diminish, or appear to others to diminish, the objectivity of professional judgment. Helpful questions for gauging whether a gift relationship is ethically appropriate include 1) What would my patients think about this arrangement? What would the public think? How would I feel if the relationship was disclosed through the media? 2) What is the purpose of the industry offer? 3) What would my colleagues think about this arrangement? What would I think if my own physician accepted this offer?

Rationale

Physicians understand that to maintain their professional objectivity they must be mindful of potential biases in medical information (7, 11). In fact, the entire infrastructure of science and much of physician education is built on the fundamental notion of eliminating, or at least controlling for, the many and powerful biases inherent in generating and interpreting scientific data. Ethically and professionally, the objective evaluation of medical information is critical for deciding on best clinical practices (beneficence) and avoiding risks to patient safety (nonmaleficence) (12–14). Thus, physicians have an obligation to themselves, their profession, and society to evaluate, correct for, and eliminate potential bias in medical information from all sources.

Recent studies and reports have examined industry influence on physician objectivity and behavior (15, 16), particularly prescribing practices, formulary choices, and assessment of medical information (3, 7, 17–25). Physicians frequently do not recognize that their decisions have been affected by commercial gifts and services (26) and in fact deny industry's influence (3, 15, 17–22), even when such enticements as all-expenses-paid trips to luxury resorts are provided (23). Research, however, shows a strong correlation between receiving industry benefits and favoring their products (23, 25, 27).

What Would My Patients Think about This Arrangement?

The dictates of professionalism require the physician to decline any industry gift or service that might be *perceived* to bias their judgment, regardless of whether a bias actually materializes. A perception that a physician is dispensing medical advice on the basis of commercial influence is likely to undermine a patient's trust not only in the physician's competence but also in the physician's pledge to put patients' welfare ahead of self-interest. Recent research on patient attitudes shows that patients are more likely than physicians to perceive industry gifts as inappropriate or influential on medical practice (19, 28, 29). More particularly, a significant number of patients believe that industry gifts bias their physicians' prescription practices and ultimately drive up medical costs. Patients make a distinction, however, between acceptable and unacceptable gifts. Most think that inexpensive incentives designed for office use (pens, notepads) and patient care (drug samples, medical texts) do not have a negative effect on health care. They are much more likely, however, to disapprove of items for personal use (radios, coffeemakers), especially as the gifts become more costly (dinners, trips) (28, 29).

What Is the Purpose of the Industry Offer?

The potential for bias in industry-prepared information becomes especially precarious when such information is accompanied by a gift or free service. Even when the amenity is medically related, a major aspect of the offer involves the establishment of a gift relationship, a phenomenon much studied in social science research. In culture after culture, there has emerged "a vivid sense of the immense pervasiveness of the social obligation" that a gift elicits (30). Social scientists agree that the prevailing purpose of the gift is to establish the identity of the donor in the mind of the recipient and to oblige the recipient to reciprocate (30–32). It is not just lavish amenities that are in question. The acceptance of even small gifts can affect clinical judgment and heighten the perception (as well as the reality) of a conflict of interest (12).

From a certain perspective, drug samples can be characterized as "gifts." Because physicians can distribute such medications to patients at no apparent cost (33), the practice may seem to promote the profession's core principle of equitable access and justice in health care. The practice does allow the patient to try out a new medication before being committed to an expense. However, the sample mainly serves to encourage physicians to prescribe the new product. Research shows that once a patient exhausts a free supply of medication, the physician typically writes a prescription for the same brand (33, 34). Because few samples are for older or less expensive products (35), higher patient costs generally result. Moreover, physicians and their families and staff use approximately one third of the samples (33, 34, 36, 37), which illustrates how the practice fosters access to physicians' offices and encourages a gift relationship.

In addition to drug samples, industry may distribute product literature or "patient care services," such as education aids or disease management software. It is understandable that, in a busy practice, physicians would welcome industry's materials and technologies to keep themselves and their patients current with the latest developments in the medical field. Physicians must keep in mind, however, that industry-supplied medical information, although neutrally packaged, is in fact promotional (4). Physicians should never rely solely on industry-provided information or services as a substitute for an objective review of the literature and understanding of patients' conditions.

What Would My Colleagues Think about This Arrangement?

The issue of industry gifts, hospitality, and subsidies arises as early as medical school and residency programs (18, 20–22, 27, 38–42). Medical students and physicians-in-training often have opportunities to receive instructional materials, medical equipment, or even educational dinner programs. While it is recognized that such arrangements can benefit the medical education experience and that medical students and residents have unique financial and work circumstances, it is also necessary to note that medical training includes instruction on professional ethics, including appropriate relationships with industry. Medical students, physicians-in-training, and practicing physicians should apply the same ethical standards to their interactions with industry (43).

Physicians do not always agree about the appropriateness of gifts. Ideally, physicians should not accept any promotional gifts or amenities, whatever their value or utility, if they have the potential to cloud professional judgment and compromise patient care. As a practical matter, many physicians are comfortable with limiting their acceptance of gifts to items that enhance medical practice or knowledge and that are of modest value. Differences of opinion will undoubtedly arise because of the ways in which an item or service is valued in different practice environments and communities. Nonetheless, such debates are important because they remind physicians of the need to gauge regularly whether a gift relationship is ethically appropriate.

Recommendations

The inherent difficulty in defining what makes a gift appropriate has, to an extent, contributed to lapses in judgment by otherwise ethical persons. It is difficult to set with any precision a monetary value that would render a gift unacceptable. There is no consensus model for determining relative value, and one will not be recommended here. Instead, some specific guidance is offered in the following examples of generally acceptable industry gifts: inexpensive gifts for office use (such as pens and calendars), low-cost gifts of an educational or patient-care nature (such as medical books), and modest hospitality (such as a reception or other food and drink) that is connected with a legitimate educational program.

Understandably, even these "generally acceptable" examples are subject to interpretation and will frustrate some readers. Together with the fundamental questions listed in Position 1, physicians should use these recommendations as guides in making a good-faith effort to evaluate the potential for influence and to determine what kinds of amenities are ethically appropriate to accept. It is unethical for physicians to accept any industry gift or subsidy that is predicated on recommending a particular product or taking a particular clinical action. The preceding examples cannot and should not be used as a perfunctory substitute for self-appraisal.

POSITION 2. FINANCIAL RELATIONSHIPS BETWEEN PHYSICIANS AND INDUSTRY

Physicians who have financial relationships with industry, whether as researchers, speakers, consultants, investors, owners, partners, employees, or otherwise, must not in any way compromise their objective clinical judgment or the best interests of patients or research subjects. Physicians must disclose their financial interest in any medical facilities or office-based research to which they refer or recruit patients.

Rationale

Like gifts, financial relationships between physicians and industry can jeopardize professional objectivity. While collaborations in pharmaceutical development and biotechnology are often effective spearheads for advancing therapies and patient care, research and investment ties can create dual commitments or conflicts of interest (12) and risk the confidentiality of patient information. Some physicians own, hold stock in, or have other financial stakes in the medical industry and biotechnology; others work for industry as researchers or are university-based researchers who receive industry grants. Increasingly, clinicians are invited to act as industry consultants or to participate in clinical trials of newly developed drugs or devices, often by enrolling their own patients as subjects (12, 44).

Ownership or Other Financial Interest in Medical Resources

Physician ownership or other financial interest in medical equipment, health care facilities, laboratories, and other medically related resources raises ethical and legal concerns that physician self-interest may lead to inappropriate self-referrals or overuse of resources. For example, one study found that physician-owned clinics generated 50% more patient visits than independent clinics, suggesting that self-referral had induced unnecessary demand (45). Because a physician's primary duty is to act in the best interests of patients, physicians cannot allow financial arrangements to influence their judgment about what constitutes an appropriate level of care. It is unethical for physicians to overutilize resources or make unnecessary referrals to goods and services for their own financial benefit. It is also unethical to participate in any arrangement that links income generation explicitly or implicitly to equipment or facility usage or revenues generated by investor-physicians. There are instances, of course, in which self-referrals are acceptable, such as in remote or isolated settings where there is a dearth of alternative medical resources. In any event, if physicians refer patients to resources in which they have a material interest, they need to disclose their financial investments and, to the extent practicable, specify alternative sources of goods and services (12).

Consulting, Speaking, or Writing on Behalf of Industry

Industry may pay clinicians well to act as consultants, speak on behalf of a company, or participate in community-based industry trials. As a rule of thumb, related payments from industry are acceptable for teaching and for research that advances medical and professional knowledge (for example, honorariums for presentations at symposiums), commensurate with the extent of the physician's services and reasonable travel expenses.

Physicians should guard against conflicts of interest when invited to consult or speak for pay on behalf of a company. It is likely that a company will retain only individuals who make statements or recommendations that are favorable to its products, thus compromising the physician's scientific objectivity. Physicians should accept honorariums only for services provided and must disclose any industry sponsorship or affiliation and other potential conflicts of interest to formal lecture audiences and publication editors (31, 46).

Physicians should also be circumspect if asked to deliver educational programming developed by a medical education and communication company. Such companies, which are largely financed through the pharmaceutical industry, are for-profit developers and vendors of continuing medical education (47). It is important that physicians retained as lecturers in such settings control the content of the educational modules they deliver rather than allow their presentations to be scripted by the company. Lecturers should screen industry-prepared presentation aids (such as slides and reference materials) to ensure their objectivity and should accept, modify, or refuse them on that basis. Presenters using such materials should disclose their source to audience members.

Paid efforts to influence the profession or public opinion about specific medical products are particularly suspect. It is unethical, for example, for physicians to accept commissions for articles, editorials, or medical journal reviews that are actually ghostwritten by industry or public relations firms in an attempt to "manage the press" about certain products or services (48).

Participation in Industry-Sponsored Research

Participation in practice-based research can contribute to our understanding of the benefits and risks of a new product, thereby promoting medicine's underlying principles of beneficence and nonmaleficence. Still, physicians are responsible for ensuring that any clinical research in which they participate is potentially of significant value and is ethically conducted (12, 49). In particular, physicians invited to join "postmarketing studies" that require the prescribing of a company's product need to consider the scientific validity of the research and its potential to enhance medical progress (44, 50, 51). Physicians should not participate in studies that are, in effect, thinly disguised promotional schemes to entice physicians to use new products.

Physicians also have an ethical obligation, based on the principle of patient autonomy and informed choice, to disclose their commercial ties to patients who are prospective study participants (12). Physicians who involve their own patients in office-based trials must also be aware of potential conflicts between what is best for the patient-subject and what is optimal for the conduct of the research. In weighing the two interests, clinicians must consider their role as physician first and as investigator second (12, 52). It is reasonable for the clinician to receive compensation commensurate with time and expenses incurred in study recruitment. However, physicians may not accept compensation simply for referring their patients to an industry study, regardless of whether the physician directly participates in the trial. Known as "finder's fees," such arrangements represent pure profit and create an inherent conflict with the best interests of the patient (12, 49, 53).

Finally, physicians involved in commercial trials must guard against bias in publishing research outcomes. Several studies show that physicians with financial ties to pharmaceutical manufacturers are significantly more likely than independent reviewers to report findings that support the sponsor's drugs; likewise, they are less likely to report unfavorable findings (48, 54–57). To maintain objectivity, it is recommended that physicians secure pre-performance agreements with sponsors ensuring that negative results will not be quashed and that findings will be made publicly accessible. Physicians should also be aware that the International Committee of Medical Journal Editors recently agreed not to publish any studies conducted under conditions in which the sponsor can control the data or prevent publication (58). If a company explicitly or implicitly encourages a physician to suppress particular outcomes, the physician must not participate in the research and should report the incident to the institutional review board overseeing the research, and to the U.S. Food and Drug Administration if the research is a drug trial.

Dealing with Institutional Product Bias

Physicians employed by managed care organizations are obligated to abide by drug formularies and practices of pharmacy benefit management. Formularies specify a list of drugs that are considered most useful and cost-effective, and managed care organizations often limit reimbursement to these drugs. Pharmacy benefit management companies, which increasingly are owned by pharmaceutical manufacturers, act as intermediaries among pharmacies, pharmaceutical companies, physicians, and third-party payers to review prescribing practices and negotiate prescription prices. Pharmacy benefit management companies have access to confidential patient records and may try to influence changes in patients' drug regimens, sometimes to reduce costs and sometimes to favor a manufacturer (59, 60). Current state and federal policies regarding third-party access are not consistent and can, at times, jeopardize the confidentiality of patient information. Cost savings are certainly encouraged, especially as a matter of justice and equity in health care. However, any agreement to change drugs should be evidence-based, not company-biased. If faced with institutional bias in drug formularies, individual physicians should be prepared to insist on waivers for unlisted drugs when it is in the best interests of their patients.

Electronic Technology

Finally, the development of "e-commerce" has led to ethical issues not envisioned in the 1990 position paper. Since that time, the importance of electronic commerce and Internet technology to the practice of medicine has increased dramatically. Health care systems in the 21st century will undoubtedly take advantage of electronic technology to collect and analyze clinical data, support consumer access to health information, and complement the physician's management of patient care (13).

As valuable as consumer access is, information provided electronically can be biased by its sponsor. To mitigate this potential conflict, physicians who have a material interest in "e-health" businesses or who interact with Internet hosts to publish their own Web sites have an obligation to control the site's medical content and regularly maintain it. Such sites should disclose all sources of industry support and clearly distinguish any commercial advertisements or sponsored content from substantive content, both in form and in placement. Physicians with commercially sponsored Web sites also need to alert users if a sponsor plans to conduct any online tracking.

CONCLUSION

The guidelines offered here identify several examples of financial and other material relationships between physicians and industry, but the list is not exhaustive. As opportunities for commercial ties continue to grow, physicians should be increasingly wary of threats to their professionalism and independent judgment about patient care. Providers of medical education and professional medical societies face similar problems of potential influence. Part 2 of this statement on industry relations will address the ethical risks and responsibilities of professional medical associations and educators.

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POSITION PAPER

Physician–Industry Relations. Part 2: Organizational Issues

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This is part 2 of a 2-part paper on ethics and physician–industry relationships. Part 1 offers advice to individual physicians; part 2 gives recommendations to medical education providers and medical professional societies.

Industry often sponsors programs for graduate and continuing medical education, as well as major events of medical professional societies. Industry is an abundant source of advances in medicine and technology and plays a crucial role in disseminating up-to-date medical information. Although industry information fills an important need, studies suggest that it is often biased.

Providers of graduate and continuing medical education have a duty to present objective and balanced information to their participants; thus, they should not accept any funds that are contingent on a sponsor's ability to shape programming. Medical educators need to evaluate and control the planning, content, and delivery of education provided under their auspices. They should disclose industry sponsorship to students, faculty, and continuing medical education participants and should adopt explicit organizational policies about acceptable and unacceptable interactions with industry.

Medical professional societies have a duty to promote the independent judgment and professionalism of their members. Organizers of industry-sponsored meetings should clearly separate product promotion from impartial medical education. Adopting specific policies for dealing with industry sponsorship can also help professional societies guard against outside influence. The American College of Physicians–American Society of Internal Medicine's core ethical principles for external funding and relationships serve as an example.

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See related article on pp 396-402.

In 1990, the American College of Physicians published a position statement titled "Physicians and the Pharmaceutical Industry," which addressed industry relations with individual physicians and medical professional groups (1). The statement was prompted in large part by evidence of the drug industry's influence on medicine and the ensuing concern for professional integrity and patient care. Since that time, the influence of industry on medical practice, research, and education has continued to increase, as have physician–industry relationships. In response, the American College of Physicians–American Society of Internal Medicine (ACP–ASIM) has prepared an updated, 2-part set of ethical positions. Part 1 (see pp 396-402) addresses individual physicians and their relationships with industry through gifts and collaborative activities. The current paper, which is part 2, addresses ethical concerns relevant to medical education providers, academic units that accept industry support, and medical professional societies.

A responsible and productive alliance between medical organizations and industry is crucial for medical progress. At the same time, providers of graduate medical education (GME) and continuing medical education (CME) and medical professional societies are also responsible for regulating their dealings with industry. These groups should evaluate their external funding relationships not only for prospective benefits but also for potential conflicts of interest and other ethical problems, such as real or perceived improprieties and bias in the materials they offer, their policies, and projects they undertake.

Given the rapid pace of technological developments and therapeutic advancements in medicine and biotechnology, both students and practicing physicians rely on education providers and professional societies for objective, up-to-date health care information. Commercially sponsored information offered in such settings can be biased in favor of manufacturers and has the potential to unduly affect the independent judgment of medical professionals (2–5). To help overcome this conflict, this paper offers two positions on the external funding of educational programming and activities of medical professional societies. The College's positions described in

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* This paper was written by Susan L. Coyle, PhD, and was developed by the American College of Physicians–American Society of Internal Medicine (ACP–ASIM) Ethics and Human Rights Committee. Members of the ACP–ASIM Ethics and Human Rights Committee were William E. Golden, MD (*Chair*); David W. Potts, MD (*Vice Chair*); Harmon H. Davis II, MD; David A. Fleming, MD; Susan Dorr Goold, MD; Vincent E. Herrin, MD; Jay A. Jacobson, MD; Risa Lavizzo-Mourey, MD, MBA (*Past Chair*); Joanne Lynn, MD; and Daniel P. Sulmasy, OFM, MD, PhD. Lois Snyder, JD, Director of ACP–ASIM's Center for Ethics and Professionalism, provided principal staff support. This paper was approved by the ACP–ASIM Board of Regents on 15 July 2001.

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part 1 are numbered 1 and 2; the positions appearing here are numbered 3 and 4.

POSITION 3. INDUSTRY-SUPPORTED GRADUATE AND CONTINUING MEDICAL EDUCATION

Public and private GME and CME providers that accept industry support for educational programs should be aware of potential conflicts of interest and should develop and enforce explicit policies that maintain complete control of program planning, content, and delivery. (This position addresses education providers that accept industry support, not industry-held educational programs.)

Rationale

Continuing medical education is a multibillion-dollar business (6), and the role of the health care industry is considerable (7). The commercial role is expected only to grow as new, for-profit medical education and communication companies begin providing CME (8). Industry support of GME is difficult to quantify but is potentially of great importance. A 1990 survey of internal medicine residency programs revealed that 90% of program directors allowed industry to sponsor educational conferences for their students; of these, 30% reported not having alternative funds for such events (9).

Continuing medical education is critically important for physicians to keep abreast of the latest developments in patient care. Indeed, physicians have sometimes been slow to adopt efficacious new therapies into routine clinical practice and therefore to improve patient care (10). Because industry is an abundant source of advances in medicine and technology, its desire to quickly disperse information about its products helps to fill an important need (11). The presentation of medical information, however, must be objective, and this becomes the responsibility of medical education providers and medical professional societies.

Commercial funding for CME usually takes the form of general course grants or speaker funds, although it is sometimes provided for hospitality and travel expenses related to educational symposiums. Many medical schools also accept commercial sponsorship of educational conferences, as well as funds for student organizations, publications, and awards (2). While support for GME and CME is often welcomed, commercial support can create an opportunity for the subtle or not so subtle introduction of bias through industry-oriented programming. For example, a study of CME courses funded by rival manufacturers showed that course contents were biased in favor of each funder's product (12). Further study showed that physicians who attended industry-supported CMEs subsequently altered their prescription practices in favor of the funder's products (13).

Education provided through a reputable academic institution or medical professional society is expected to offer expert teaching and "best evidence" information (14). However, professional impartiality about what constitutes best evidence can be tested if industry selects the teacher or underwrites the program. To enhance the impartiality of CME, groups such as the Accreditation Council for Continuing Medical Education (ACCME) have recommended guidelines for relationships between educators and industry (15). The guidelines advise CME providers to plan for balanced program content and ensure that their programs are free of commercial bias for or against any product or service. While the ACCME guidelines are a step in the right direction, commentators have noted that they are not difficult to skirt (3, 8).

Medical education organizations have an obligation to the profession and society to evaluate and correct for potential bias. When faculty or speakers must use trade names in a GME or CME presentation, they should cite similar products or services of several companies rather than focusing on a single supporting company. Faculty, deans, and program directors should also promote sensitivity to potential biases by providing specific education to help their students, physician trainees, and medical fellows evaluate industry-provided information. For education and sensitivity training to be successful, however, faculty must act as positive role models. Chief residents and medical school faculty members should set ethical examples to students by conducting their relationships with industry in a highly principled manner and disclosing their own commercial ties.

Medical education providers must also administer the budgets of any programming provided under their auspices. If an organization allows industry-sponsored hospitality, the hospitality should be modest and arranged so that social activities do not compete with educational events (15). Providers of CME must also control access to registrants' mailing addresses and should disclose any commercial support to registrants through general program materials. Providers should ban the distribution of promotional materials in educational sessions unless the materials are clearly related to instruction.

Medical education programs are also responsible for discussing industry sponsorship with invited speakers, including support for such presentation aids as slides or literature reviews. This disclosure will give speakers the opportunity to screen the aids and accept or refuse them (16), or make modifications to ensure objectivity. (Speakers who use industry-developed aids should disclose that information to the audience.) In addition, faculty and program directors should disclose any support they receive individually as consultants, investigators, or shareholders, and they should be sure that their relationships are explicitly listed in the CME program (16, 17). Finally, faculty and program directors may accept industry honorariums or subsidies only for services rendered and, if applicable, reasonable travel expenses.

In sum, it is unethical for academic institutions and educational organizations to accept any support that is explicitly or implicitly conditioned on industry's opportunity to influence the selection of instructors, speakers, invitees, topics, or content and materials of educational sessions. To reflect this position, medical education providers should adopt and enforce specific organizational policies about acceptable and unacceptable interactions with industry (9).

POSITION 4. SUPPORT FOR MEDICAL SOCIETY ACTIVITIES

Medical professional societies that accept industry support or other external funding should be aware of potential bias and conflicts of interest and should develop and enforce explicit policies that preserve the independent judgment and professionalism of their members and maintain the ethical standards and credibility of the society.

Rationale

Medical professional societies share the physician's duty to advocate and act in the best interest of the patient and society, and they are expected to serve as independent and trustworthy sources of health care information and education for members and the public. In developing specific projects or meetings to achieve these goals, many professional associations seek external funding to defray costs. While such arrangements are legitimate, they can result in dual commitments or conflicts of interest. External funding has the potential to alter an organization's agenda, influence its policy positions, or weaken its credibility (18). To avert potential conflict or bias, which in turn may affect members, professional societies need to adopt specific institutional policies governing their relationships with industry.

One of the premiere events of the medical professional society is its annual or semiannual membership meeting, at which scientific sessions, symposiums, workshops, and exhibitions are offered to disseminate medical knowledge and enhance clinical skills. Such meetings offer excellent opportunities to educate members about issues of bias in medical information and to present ethical positions on physician–industry relationships. These meetings usually also offer the opportunity for commercially sponsored exhibits and events.

Physician organizations and professional societies need to conduct professional meetings in a highly principled manner. To be sure, industry's presence can have positive effects. Industry is a significant source of innovative development in medicine and is responsible for informing physicians about the benefits (and risks) of promising diagnostic and therapeutic discoveries. However, industry presence at medical society events may divert interest from the scientific agenda and detract from the meeting's focus on professionalism and other organizational goals. In addition, industry attractions create potentially fertile ground for providing biased medical information. To lessen this possibility, meeting organizers should ensure that product promotion activities are separated from impartial medical information. Presentation of industry findings and product developments, whether through displays or teaching exercises, should take place only in designated exhibition space or in funded lectures that the program clearly identifies as being independently organized and separate from official scientific sessions.

To help preserve members' independence of views, medical societies also need to ensure that meeting programs are balanced and reflect the needs and interests of members and patients, not sponsors. To prevent any real or apparent corporate favoritism, and to stay true to the organization's core missions, medical professional societies should avoid endorsing specific products and services. ACP–ASIM policy, for example, sets out specific criteria for vetting requests for corporate endorsements to avoid influencing internal policy or promoting an agenda to serve external interests. Other medical professional societies are encouraged to adopt such internal policies.

Professional groups should also develop policies to guide the acceptance and disclosure of industry and other external funding and to avoid reliance on outside sources of support. The College recently adopted a set of core ethical principles to guide its dealings with external funding sources and to serve as an example for other professional societies as they develop their own policies. These principles can be found in the Appendix.

CONCLUSION

The positions discussed here and in part 1 are derived from medicine's basic responsibilities to advocate for and protect a patient's best interests and pave the way for informed choice. To these ends, medical education providers and medical professional societies should avoid all industry interactions that might diminish, or appear to others to diminish, their objectivity or concern for patients' best interests. To do otherwise is to endanger the integrity of the profession and the public confidence it enjoys.

APPENDIX: ACP–ASIM CORE PRINCIPLES FOR EXTERNAL FUNDING AND RELATIONSHIPS, AS APPROVED BY THE BOARD OF REGENTS ON 15 JULY 2001

Commercial, government, foundation, and other funding and relationships can help the College promote its goals and its mission of enhancing the quality and effectiveness of health care. However, some financial arrangements might bias, or be seen to bias, the College as an independent, trustworthy, and credible source of health care information, policy, and education.

The following principles should guide financial and other relationships with outside organizations. (See also the College's corporate endorsement and conflict of interest policies. To obtain copies, contact Lois Snyder at 215-351-2835.)

1. The College's values, its mission, and its commitment to professionalism and excellence in medicine must drive all external relationships and externally funded activities.
2. Relationships with external organizations and funders should promote the health and welfare of the public or patient care. Member benefits resulting from external arrangements should enhance professionalism and physician practice.
3. In representing the College in external relationships, College leadership and staff must adhere to the values and ethical standards of the organization and should act to promote professionalism and trust in the organization and the medical profession.
4. External funding arrangements and external relationships must be disclosed to relevant parties on a regular basis and with sufficient detail and visibility to allow concerned parties to reach independent conclusions about potential sources of influence and real or perceived conflicts of interest.
5. Specific instances in which a financial arrangement or relationship might have the potential to influence the College's actual or perceived independence, credibility, and trustworthiness should undergo College review to minimize or eliminate such influence.
6. The College should monitor its overall reliance on commercial sources of funding and ensure that its core activities could continue if such support were diminished.

From the American College of Physicians–American Society of Internal Medicine, Philadelphia, Pennsylvania.

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ON BEING A DOCTOR

Blockers

The guy's an iceberg. I feel the cold breeze the moment I walk into the office, where he stands beside the examining table, his arms crossed, a thin man, pale eyes, dour face, measured stare. I'd say he's about 40 and prematurely bald.

Maybe iceberg isn't right. How about an oven? I get the feeling he might explode at any second. Or minefield. That's it; he's a walking minefield. I've heard there are millions of mines left over from the war in Western Europe, tens of millions in Southeast Asia. Here on Long Island, we have minefields, too, but they're not from the war. They just grow, like potatoes. They're metaphorical.

The man's handshake slides quickly away. Thus far, all I've said is, "Good morning, Mr. Lindsay, I'm Dr. Ritter." Thus far, he's nodded half an inch.

Turns out Lindsay is a neuroscientist who works at the university. He likes to be called "Doctor"—my first mistake of the day. His physician retired a couple of months ago, and he wants to "establish care" with a new internist. Turns out he's on four medications, three for blood pressure that "nobody can get to go down" and one for cholesterol. He's 38 years old. As far as I can tell from the verbal synopsis, he's never had a symptom.

"I want tests, too," Lindsay tells me. "I want a complete panel."

Well, my work's cut out for me this time. Or, rather, it's not cut out—I have to do the cutting. Reminds me of a movie the kids and I saw a few years back, about a Neanderthal man frozen in an ice block at the bottom of a ravine or something. Against all odds the guy is still alive, and the scientists figure if they warm him slowly he'll be okay. Very, very slowly. His eyes flicker. His face twitches. Soon he's back to a hundred percent, except for a broken heart because his friends and family died 40 000 years ago. If I can do the same with Lindsay, chip first, thaw slowly, maybe he'll flash a smile and tell me the whole scoop. Maybe I'll learn his language, and we'll bond, and his blood pressure will plummet. Who says imagination isn't the key to good medicine?

Turns out Lindsay doesn't want to talk about anything except numbers. You'd think he'd check his own blood pressure, being a scientist and all, but he doesn't. What he does do is remember test results. Cholesterol, potassium, you name it. Like I say, the man is as thin as an axon. And he works out, swims, eats fish twice a week, and anti-oxidizes.

"How are things?" I ask. "How's it going?"

"Listen to me," Lindsay says. "It doesn't make sense. 190 over 110, same as last time, same as the time before that. I take the beta-blocker, I take the calcium-channel blocker, I take the ACE inhibitor. Nothing makes any difference. Why? You tell me, you're supposed to know. Why doesn't it make any difference?"

"I don't know."

My belly tightens, sensing Lindsay's pressure. The man is a pressure cooker, that's what he is. About to burst. I remember working my way through college at the open hearth mill at Wheeling Steel—first, the long siren, then the thud of an explosive charge to tap the mouth of the furnace, and then the cascade of molten steel bursting from the furnace, the flaming roar of liquid steel filling ingot molds. *What makes a difference in anything?* I ask myself. And immediately respond, *Coffee makes a difference.* It's after ten and I haven't had breakfast.

This goes on for half an hour. We review the basics. Indeed, the basics show that his pressure is incorrigible. I give him new prescriptions. "This time," I explain, "we'll take it easy."

He comes back frequently for a year or so, never sick, but his pressure . . . well, maybe it gets better, but I have to admit that it's stretching the truth.

"How do you feel?"

"Fine."

"How's your wife doing?"

"Okay."

"How's work?"

"Work isn't the issue," Lindsay tells me. "My blood pressure is."

"Well, yes, but . . ."

"Either 180 over 106 is really a problem or it's not a problem. If it's not a problem, I don't see why I need to take all these drugs. If it is a problem, we're not getting anywhere."

My brilliant reply, "We just have to keep at it."

I learn that Lindsay works on gamma amino butyric acid (GABA) receptors. He slices and dices them. As I recall GABA is a neurotransmitter that suppresses certain types of messages. A neuron wants to say YES! But a GABA molecule comes along and makes the neuron say NO! Maybe that's it—that stuff is suppressing my simpatico. Every time a pulse of empathy appears, here comes a GABA ray to shoot it down.

This goes on for another few months until Lindsay disappears, and I learn by the grapevine that, intense though he was, he hadn't been getting the grants and didn't get tenure. So what happens to a discarded neuroscientist? No way can I visualize Lindsay's tense face and checked shirt flourishing in industry, where the pressure must be even worse. Instead, I imagine him joining the faculty of a small college in Iowa, teaching two or three courses twice a year and loosening his belt.

And then I come across the flyer. There it is—a not-too-sharp photograph of "the well-known Dr. Brent Lindsay," whose free lecture on "Five Steps to Finding Your Inner Strength" took place last Tuesday night at the public library. Dr. Lindsay, the flyer explains, is an eminent neuroscientist and author of numerous articles on how to achieve optimal health by directing your neural energy. He recently lectured at the Center for Holistic Medicine in Milwaukee. I recall him telling me that his wife came from Milwaukee, because in one of my attempts to thaw him (slowly, slowly), I asked if he liked the Brewers, but he had no idea who or what the Brewers were. This is the kind of point that sticks with me. "Everyone Welcome! Refreshments will be served."

My receptionist's friend told her the lecture was wonderful. Turns out that you can order Lindsay's entire kit on optimal health for $29.95 at his Web site and you'll never stop thanking yourself. Or you can order it by mail. His post office box is in St. James. Just down the road. What do you know? The guy is still around.

Some weeks later Lindsay comes in to ask if I'm interested in becoming his doctor again. Now what kind of a question is that? It seems he doesn't have any insurance these days, and he has no regular job, although his wife is still attached to the Visiting Nurses. But she works on contract without benefits. He wants a checkup, hasn't been to a doctor in a year or two, too busy. He runs his own business now. Shows me the brochure, "Five Steps to Inner Strength." This one has a picture of an idyllic mountain landscape.

"Hey, no mountains on Long Island," I remark.

Lindsay moves his facial muscles, smiles. It takes less than a minute to feel the difference—no block of ice, no minefield, no pressurized furnace. He also wears a suit, charcoal gray, and neatly patterned tie. Always before he came to the office in khakis and those red checked shirts that make you imagine icy mornings and steaming flapjacks. Also, he has on leather shoes.

"Just a scene, doc," he quips. That's right, he quips, for God's sake. "It's more like an inner landscape."

Turns out he went for a few months to an ashram, where he met "my friend, a real genius," who lives in a house built by his own hands on a hill in Oregon. This guy gave Lindsay the "miraculous gift" of confidence to look within and find wisdom. In fact, the friend also taught him how to market the wisdom, because, as he says, "truth is for sharing." So far it's working out okay, lots of lectures, lots of down time, too, but on the plus side, he already has two employees working out of the shop in his garage.

Lindsay's blood pressure reads 124 over 72, rechecked twice, a perfect reading, and as I said he more or less feels normal. That is, "normal" to me, as opposed to icy or pressurized. To him, he feels far above normal, like the idyllic scene.

"I always knew the key was inside me," Lindsay says. "The first step to finding your inner strength is to stop blaming others for pain and disappointment."

I notice he's put on a few pounds. There is also a whiff about him, cologne or after-shave.

"Taking your meds?" I ask.

"No," he smiles. "I've given them up. Blockers, inhibitors, anti-this, anti-that, who needs it? The thing is, all my life my neural energy was blocked, and it just kept getting worse, and your beta-blockers and blocker-blockers . . . you might say they blocked me from discovering my inner resources, from exploiting my inner strength."

I don't know what to say. In fact, what happened was, Lindsay lost his job. If anything was blocking his inner whatnot, it wasn't the drugs. *Take it easy,* I tell myself. So we talk about this and that, especially tai chi, which he is in the process of learning.

It's true; whatever was blocking Lindsay has cleared out and left the field wide open.

At the end of our visit, he asks me if I want to sign on. (The third step to finding your inner strength is assertive communication.) "I need someone on my team to do vitamins," he explains, "Maybe write a piece or two each month for the Web site, a pamphlet or something, answer questions . . . I don't know, we'd have to work it out."

"Thanks." I'm genuinely confused. "Thanks for thinking of me, but I'm pretty tied up these days."

"Yeah, 'tied-up' is right," Lindsay says. "But that's the thing, isn't it? Being tied up, or bound up, or blocked up . . . But if you were just to look at it, like, simply . . . I mean without any preconceptions, it would all be plain, wouldn't it? Plain and clear."

"What do you mean?"

"Just give it some thought," he says and hands me his card.

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AD LIBITUM

HUP 2,3,4

The peep-peep-peep from the hallway
is not a fluffy chick, under incubator,
but some measure of infusion or rhythm
holding the line between earth and heaven's reward (so, is earth a punishment?).
The hiss of air from the room vents is its accompaniment
never skipping a beat, supporting the concerto with soothing constancy.
I have been here through far too many movements with not a break for applause.
Across the street, Franklin Field stands guard under the overly moist skies.
Graduation day.
Wet, black gowns marking an end and beginning.
The cheering section went home before visiting hours were over.
Medicine is as relentless as loneliness.

Now, the darkness and I are left
to squabble over pointless things.

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LETTERS

The Crisis in Local Institutional Review Boards

TO THE EDITOR: As members of the institutional review board (IRB) committee that reviews adverse events for the clinical studies at our institution, we read the perspective by Burman and colleagues (1) with interest. We agree that ideally local IRBs cannot and should not be responsible for the detailed review of all safety reports in multicenter trials. However, we do not agree that we are presently exempt from the responsibility to review and question the clinical events that occur in these trials.

At our institution, we have set up a computer tracking system of all events and have reorganized our adverse event submission form. This allows our committee to review the hundreds of events in an organized format. We are thus able to detect trends of concern. If a trend is detected, we ask the investigator to obtain more information from his or her sponsor and often ask that the consent form be modified. We also plan to use this tracking system to provide a complete list of adverse events for each protocol in order to assess risk and benefit when performing the continuing review of ongoing studies.

We agree that all multicenter studies should be required to set up data and safety monitoring boards that will function without bias. The reports of these boards can be reviewed by the local investigator and then sent to the local IRB. Until independent boards are required for all multicenter studies, we believe that we must continue our own detailed review, despite the inordinate amount of time devoted to the process by our IRB office staff and committees.

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Note: Dr. Siegel is currently at Thomas Jefferson University, Philadelphia, Pennsylvania.

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1. Burman WJ, Reves RR, Cohn DL, Schooley RT. Breaking the camel's back: multicenter clinical trials and local institutional review boards. Ann Intern Med. 2001;134:152-7. [PMID: 11177319]

TO THE EDITOR: The papers by Burman and colleagues (1) and Levine (2) highlight problems in clinical research. However, there are additional factors. None of the suggestions in these papers seem to enhance the IRB's protection of research subjects.

The IRB workload has increased enormously (3), but this is not due solely to the increase in the number of multicenter clinical studies. Investigator-initiated trials and study complexity have increased, resulting in the need for expertise in evaluating the studies and methods for suitably explaining protocols to prospective subjects.

One major problem is emphasis on regulation and paperwork, often at the expense of other activities. Institutional review boards are buried in paper, and the focus is on satisfying regulations. Many times, truly important IRB functions have become secondary. Thus, there is a preoccupation with the wording of informed consent forms. Although some IRBs require that these forms not exceed an 8th-grade reading level, subject comprehension is dismal (4); it does not appear that we are making significant progress. More important than specific wording, the IRB should actually require the subject's consent, not just at enrollment but afterward, to ensure that he or she realizes the experiment is ongoing and that the therapeutic misconception does not contaminate the investigator–subject relationship. This would be an ideal function for the local IRB, whose members could obtain consent in an unbiased and knowledgeable manner. Protocol review and approval could best be managed by a central board, with the local board providing continuing oversight and an emphasis on informed consent processes.

The current academic IRB membership is largely recruited from the faculty, as with other committees, but the IRB is not another committee. It is a regulatory body charged with specific legal functions. Members of IRBs, no matter how well intentioned, must possess specialized knowledge and understand the regulated IRB functions. Inadequate compensation and education of IRB members no doubt contribute to the feeling of frustration and disillusionment, but the time commitment for the IRB far eclipses that for other academic committees, and little academic recognition is given for this work.

Creative approaches will be required to ameliorate current deficiencies. Present reliance on documentation of the process of human subject protection rather than the process itself must be changed. The U.S. Office for Human Research Protection has indicated that subject protection and fulfillment of the IRB mandate may evolve into more effective models.

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TO THE EDITOR: Burman and colleagues (1) and Levine (2), in discussing the crisis affecting protection of human research subjects, debate the relevance of expansion of multicenter randomized clinical trials. Neither paper, however, mentions a central reason for this expansion (3). Clinical trials are big business. Most trials reviewed by our hospital IRB are multicenter industry-sponsored studies; regrettably, many are not revolutionary in nature. These studies monopolize limited IRB resources.

Revolutionary trials, those with high social and scientific value, should receive priority review by IRBs. Social or scientific value is considered one of the seven requirements of an ethical trial (4). Lowering the priority of seemingly low-value investigations might help to alleviate strained IRB workloads by discouraging profit-motivated study of "me too" agents. Such prioritization could be coordinated by the central IRBs that Burman and colleagues support (1).

Furthermore, to ensure subject autonomy in the consent process, we must ensure the social and scientific value of research trials. Except for a narrow segment of research, potential benefits of a research trial are said to accrue to society, with no benefit to individual study subjects (5). In relying on subjects' altruism for most studies, as allowed by the principles of the Declaration of Helsinki, we must be proactive in measuring the value of research studies. There must be assurance that clinical research remains beholden to society, rather than to stockholders in industry.

I agree with Levine (2) that the rhetoric of criticism toward IRBs should be subdued. To ensure the ethics of clinical trials, we must examine the business of clinical trials, which are not regulated by local IRBs even after heightened attention to financial conflict of interest. Current federal effort to increase IRB regulation misdirects focus from ensuring that industry-sponsored trials are useful in design, analysis, and reporting. Members of IRBs should not be frustrated in their effort to review trials that are revolutionary and useful.

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IN RESPONSE: We are gratified that our paper generated long overdue discussion about the crisis in local IRB function. We hope that the recommendations from the National Bioethics Advisory Commission on human subjects protection and IRB function (1) will promote further discussion and bring about meaningful changes. The Commission clearly recognized the impossible demands on local IRBs in the present system, and their recommendations should improve protection of patient safety while decreasing the inefficiencies in the present system. The Herculean efforts of Dr. Siegel and colleagues to track and interpret the onslaught of adverse event reports from multicenter trials fulfill current reporting requirements but are very unlikely to add to patient safety. The regulations should be changed to clearly place the responsibility for evaluating adverse event reports from multicenter trials on the data center and the data and safety monitoring board.

Dr. Sugar states that our proposals would improve the efficiency of the IRB system but do nothing to improve the protection of research subjects. We counter that these two aspects are closely linked and that improved efficiency is essential if we are to better protect subjects' safety. We agree with his concerns that many consent forms do not effectively communicate with prospective participants (2) and that some of the most worrisome lapses have been in the process of obtaining informed consent (3). However, we suspect that most local IRBs cannot even consider enhanced oversight of informed consent discussions because they are scrambling to keep up with the flood of paperwork from multicenter trials. Ineffective regulations must be eliminated so that local IRBs have the time to monitor the process of obtaining informed consent. Finally, Dr. Sugar appears to propose that IRB members personally obtain informed consent from research participants, a task we believe impossible.

Dr. Nagy-Agren suggests that the resources of local IRBs are monopolized by industry-sponsored trials that do not significantly advance the science of medical care. While we agree that research involving "me too" agents is not revolutionary, we do not dismiss this research, nor would we suggest that central IRBs become the arbiters of clinical relevance. "Me too" agents may not revolutionize medical science, but they do provide the competition that can result in less expensive treatments. Institutional review boards are charged with evaluating whether the risks to participants in a clinical trial are reasonable, not with determining whether the trial's hypothesis is revolutionary.

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Should We Screen for Depression in Primary Care?

TO THE EDITOR: Reading the article by Valenstein and colleagues on the cost-utility of screening for depression in primary care (1), I was led to wonder about the cost-utility of the procedure I usually follow in similar circumstances.

Using the old adage that "the depressed patient sounds depressed, says he is depressed, and depresses the interviewer," I tend to listen to my patients, meanwhile asking myself, "How might this patient be feeling to say what he or she is saying and look as he or she does?", and "How am I feeling as this conversation progresses?" When there is a lull in the conversation, especially if my answers to the first two questions are that my patient sounds depressed and that I am feeling low, I tend to ask the magic question: "How's your mood?" or even, "Do you think you are depressed?" In fact, I seem to remember some expert suggesting that "Do you think you are depressed?" is the best single question to help us diagnose depression in our patients.

It's hard for me to estimate the cost of this procedure, and I am willing to believe that I too miss the diagnosis with many depressed patients. But I still wonder if asking the questions that we try to teach our first-year medical students, such as "How are you feeling?" and "What do you think is the problem?", might save some of the excessive cost of diagnosing depression.

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IN RESPONSE: Although many patients do not recognize or voluntarily admit symptoms of depression, Dr. Platt reminds us that compassionate and alert physicians can often detect these initially "hidden" depressive disorders. In such cases, formal case-finding instruments may be unnecessary or serve only to confirm suspected diagnoses. The U.S. Preventive Services Task Force does not recommend formal depression screening but does recommend that clinicians maintain a high index of suspicion for depression—in essence recommending, as Dr. Platt does, that physicians diagnose depression through a careful history (1). Yet many patients with depression remain undiagnosed and many patients who are diagnosed receive inadequate treatment (2).

Given this situation, health care organizations have considered ways of assisting physicians in diagnosing or treating depression more effectively, usually through educational programs or formal depression screening. Less often, organizations have offered intensive interviewing courses, particularly to trainees. (Intensive interviewing courses have shown promise in increasing the detection of depression in one study [3], but the costs of providing this training and the frequency with which it must be offered are unclear.) Health care organizations have seldom implemented multimodal programs to increase the effectiveness of depression treatment.

In our article, we note that meticulous attention must be paid to both the costs of intervention to increase detection and the effectiveness of treatment. From the tone and content of his letter, we suspect Dr. Platt is highly adept at identifying depressed patients and is also adept at communicating these skills to students. If Dr. Platt and his students efficiently identify depressed patients within the context of a thorough interview and provide effective treatment—by carefully educating their patients, monitoring them closely after treatment initiation, paying close attention to issues of adherence, changing antidepressants when response is inadequate, and appropriately referring patients to mental health specialists—their interventions are likely to be highly cost-effective (4). However, some physicians may be less adept at identifying depression, and most physicians require support to provide the complex but essential components of depression treatment. Even after extensive education, physicians who do not receive systematic support for treatment have difficulty maintaining optimal practices (5).

We commend Dr. Platt for his efforts to train young physicians to carefully listen to their patients and remain alert for depression. However, without organizational support for systematic follow-up, highly attuned physicians or repeated screening programs can add only limited value.

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Misconceptions about Lyme Disease: Confusions Hiding behind Ill-Chosen Terminology

"The beginning of wisdom is to call things by their right names."

—Ancient Chinese proverb

Nomenclature influences perceptions of reality and frames ensuing discussions. Imprecision contributes to misinterpretation of observations and studies, altering clinicians' approaches. The impact of imprecision and novel reinterpretation of terminology can be seen in the Lyme disease debate. A quarter century after its initial description, a review of the terminology contributing to confusion about Lyme disease is needed.

Lyme disease is treatable and curable with antibiotics (1–4), especially if treated promptly, usually with an excellent long-term prognosis. The term "promptly" taken out of context suggests one *must* treat without any delay. In fact, even untreated patients have a good prognosis. A 10- to 20-year follow-up of patients at Yale's Lyme Disease Clinic from 1976 to 1983, many of whom were not treated for early Lyme disease, shows that the patients with erythema migrans did not differ from normal controls in current symptoms, physical findings, results of neuropsychological testing, or responses to the Short-Form 36 Health Assessment Questionnaire (5). However, significant long-term sequelae occurred in patients with untreated facial palsy who probably had disseminated Lyme disease at initial evaluation and probably required intravenous therapy (5).

"CHRONIC LYME DISEASE"—A TERM IN SEARCH OF DEFINITION

Despite this generally optimistic picture, claims of persisting infection and antibiotic unresponsiveness have contributed to anxiety. "Chronic Lyme disease" (6, 7) is a common clinical diagnosis in some geographic areas (8, 9) and is based on thinking that is at odds with scientifically validated findings. No objective physical findings or unique historical features define "chronic Lyme disease," a term used by support groups and their few physician allies, not the academic medical community. Although the subject of much debate, "chronic Lyme disease" is not well defined. The term is usually applied to patients with symptoms, such as fatigue, achiness, malaise, and difficulty with concentration and memory, after treatment of documented Lyme disease or illnesses thought to be Lyme disease, or in patients without preceding illness (9). Once the term Lyme disease is applied, it *is* Lyme disease, forever and irrefutably, a diagnosis often "reaffirmed" by cross-referral between "Lyme literate" physicians.

Many patients receive repeated courses of antibiotics, with transient or waning responses, leading to more or a combination of antibiotics. Occasionally, this course of treatment can go on for years, with little relief. Originally, "chronic" was used in the context of Lyme arthritis, which, in the era before it was determined that Lyme disease was responsive to antibiotics, persisted for years, finally resolving spontaneously (10). Antibiotics are of proven value for Lyme arthritis (11); treatment of early Lyme disease usually prevents arthritis.

A Nexis-Lexis review reveals that "chronic" was first applied to Lyme disease in 1985: Lyme disease was "a potentially chronic and debilitating illness transmitted by tick bites" (12). In 1986, "chronic" referred to outcomes if antibiotics were not administered (13). A letter to the editor by Drs. Falvo and Nadelman urged more support for research: Lyme disease could cause "birth defects, fetal death, unilateral blindness, and chronic debilitating arthritis" (14) (the first and second occurrences still unproven, the third rare, and the last well reported). An adjective appropriate for Lyme arthritis before the identification of antibiotic responsiveness (1, 2, 10, 11) was used to describe patients not responding to antibiotics, suggesting that antibiotics do not kill *Borellia burgdorferi.*

Some Internet sites, support and advocacy groups, and some clinicians claim that the truth is deliberately being obscured: that "chronic Lyme disease" is far more common than the authorities allow us to know; antibiotics are often not curative; infection can be controlled only by long-term antibiotic therapy, often more than insurance companies allow; serologic tests are inaccurate and often yield falsely negative results, thereby incorrectly discouraging diagnosis; the prognosis is not nearly so rosy as "they" (the nefarious academic experts) claim;

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Table 1. **What Is Accepted about Lyme Disease**

Lyme disease is also known as Lyme borreliosis and occasionally as erythema migrans disease.

Lyme disease is a multisystem inflammatory condition of the temperate Northern hemisphere caused by spirochetes collectively known as *Borrelia burgdorferi* sensu lato.

Borrelia burgdorferi sensu lato consists of three pathogenic genospecies: In the United States, Lyme disease is caused by *B. burgdorferi* sensu stricto; in Europe and Asia, Lyme borreliosis is due to infection with *B. garinii*, *B. afzelii*, and *B. burgdorferi* sensu stricto.

Lyme disease is spread by *Ixodes* ticks: *I. scapularis* in the northeastern, north midwestern, and Middle Atlantic states of the United States and *I. pacificus* along the northern Pacific coast; *I. ricinus* in Europe; and *I. persulcatus* in Asia. (*I. scapularis* is also found in the southeastern United States, but little if any Lyme disease is reported from that region.)

Most reported cases of Lyme disease in the United States are from southern New England, the Middle Atlantic states, Wisconsin, Minnesota, and northern California. Scattered cases have been reported from the upper South and the Midwest. Erythema migrans–like lesions have been reported from other regions, such as North Carolina (15) and Missouri (16), without serologic confirmation of exposure to *B. burgdorferi*.

Lyme arthritis was described in studies of an outbreak of presumed juvenile rheumatoid arthritis in Connecticut; the association with preceding erythema migrans (then known as erythema chronicum migrans) and tick bites became apparent soon thereafter.

As nonarticular features were identified, the spectrum of Lyme disease became clear and the similarities of Lyme disease with clinical findings from erythema migrans in Europe emerged.

After identification and cultivation of pathogenic borrelial genospecies from tick and human specimens, serologic tests measuring anti–*B. burgdorferi* antibodies were developed and criteria for their interpretation were established.

The clinical spectrum of Lyme disease includes effects on the skin, heart, peripheral and central nervous systems, and the musculoarticular system; these effects have been reviewed elsewhere (1, 2, 5, 7, 10, 17).

Lyme disease has been described using three phases of infection:

1. Early localized disease: erythema migrans and associated symptoms
2. Early disseminated disease: multiple erythema migrans and associated symptoms; Lyme carditis; neurologic features, including facial (and other cranial nerve) palsies, lymphocytic meningitis, and radiculoneuropathies
3. Late disease: neurologic features, including peripheral neuropathies and chronic mild encephalopathy; arthritis, including migratory polyarthritis and/or monoarthritis

The pathogenesis of Lyme disease is not entirely understood, but some of the features of Lyme disease depend on the presence of the organism at the site of damage. Immunologic mechanisms, summarized elsewhere (18), may underlie other features of the disease.

many lives have been ruined; and many people have died (8–10). None of these claims is supported by scientific medical literature, yet they disseminate regularly, acquiring verity by their repetition.

By focusing on terminology, we may understand how some confusion has been promulgated and exacerbated. Insight may aid in clarification and be useful in addressing non–Lyme disease areas of contention. The contents of **Table 1** are probably acceptable to most researchers and clinicians who think about Lyme disease. Beyond these "absolute" facts lie concepts involving terms such as "very unlikely," "has been reported," "usually," or "in most patients"—modifiers describing "shades of gray." Physician-scientists are good at communicating facts, but "shades of gray" are often difficult to convey; the more precise one tries to be about the limits of our knowledge, the more doubts are planted, and the more misinterpretations occur. This is the root of endless debate, the home of a Cartesian dualism of sorts.

RATIONALISTS VERSUS EMPIRICISTS

The opposing sides in this debate about the true nature of Lyme disease can be described as "rationalists" and "empiricists." Rationalists use scientific studies, both clinical and molecular, to develop models of disease and appropriate diagnostic and therapeutic responses. Empiricists base models on community events, developing diagnostic and management schemas that are compatible with observations, but often at odds with scientific conclusions. In conveying their message, empiricists often adopt terminology that contradicts the terminology's intended meaning. Most published clinical and basic research on Lyme disease is from rationalists, physicians searching for objective evidence of infection. The empiricists' ranks include support groups and physicians in practices devoted to the care of patients with "chronic Lyme disease," who are given a diagnosis and are treated on the basis of nonspecific symptoms, such as fatigue, cognitive dysfunction, and pain, rather than objective evidence of infection. Empiricists "listen to the patient" rather than follow the advice of scientific studies, as if these were mutually exclusive. Rationalists fear that physicians, with the help of misinterpreted test results, occasionally misdiagnose serious illnesses as "chronic Lyme disease." Empiricists often diagnose without formulating a differential diagnosis—this *is* Lyme disease. Some call these two opposing views "two schools of thought," but I prefer to call them proponents of "reality" and "alternative reality." The sage of Baltimore, H.L. Mencken, could have been referring to this divide when he penned his introduction to the first American edition of *The Antichrist* by Nietzsche: "The majority of men prefer delusion to truth. It is easier to grasp. Above all, it fits more snugly into a universe of false appearances . . . ."

"Delusions" may satisfy needs; facts offer cold comfort to the sufferer. When false appearances assume the cloak of "reality," "alternative reality" is established.

The debate between these two groups includes diagnosing the illness, use of testing in diagnosis and management, duration and forms of therapy, prognosis, and defining a cure. Inattention to details and facts, their manipulation, and incorrect citation have fed this occasionally rancorous disputation (12), further confusing most clinicians and patients on the sidelines and causing the suffering of innocent patients and families.

LYME DISEASE AS "THE GREAT IMITATOR"

The term "The Great Imitator" as applied to Lyme disease (an attempt to form an analogy with another spirochetal disease, syphilis [19]) contributed to confusion. The comparison was meant not to denote clinical similarities between these diseases but to suggest that, as with syphilis in a previous era, Lyme disease included a broad range of findings and mimicked other diseases. However, it soon became clear that most cases of Lyme disease are recognizable in a well-described spectrum (20–25), the rare exceptions being, by definition, outliers (26). Most patients have objective abnormalities (2). Used correctly, testing is helpful: Immunologic (antibodies in serum and cerebrospinal and synovial fluids) (27), molecular biological (polymerase chain reaction identification of specific DNA), electrophysiologic (heart and neurologic), and neuropsychological (28) tests can support the diagnosis (8). Instead, "The Great Imitator" was misinterpreted as suggesting that Lyme disease routinely mimics and is mimicked by many other diseases. Some empiricists believed Lyme disease was difficult to explicitly diagnose and had to be part of the differential diagnosis of *all* problems of *all* diseases it *might* imitate (11). Lyme disease is often considered in many patients whose symptoms do not explicitly suggest Lyme disease and who receive that diagnosis merely because no other diseases can be explicitly diagnosed.

CENTERS FOR DISEASE CONTROL AND PREVENTION CRITERIA: USE AND MISUSE

The belief that Lyme disease is often overlooked is expressed as dissatisfaction with (even anger at) the Centers for Disease Control and Prevention (CDC) surveillance criteria as dangerous stricture, inexplicably designed to minimize reports of "accepted" cases (29). The criteria were designed for surveillance (and are useful as entry criteria for studies) but were not meant for diagnostic purposes. Tabulation of cases that satisfy criteria allows comparison from year to year, assessing numeric and geographic expansion. Not all cases meet the criteria (30).

"LYME DISEASE IS A CLINICAL DIAGNOSIS"

The original meaning of "Lyme disease is a clinical diagnosis" was that one should not diagnose solely on the basis of test results but also on historical and physical evidence that explicitly suggests Lyme disease. Such findings should suggest *the possibility* of Lyme disease—no finding, even in endemic areas, is diagnostic. The phrase has been manipulated into something far from its original intent. History and physical examination may not suggest Lyme disease, serologic testing may yield negative results, but one makes a "clinical diagnosis" simply because one decides the nonspecific symptoms (for example, fatigue and achiness) are due to Lyme disease: The "patient had symptoms compatible with Lyme disease" and lived in an endemic area. Lyme disease becomes a "diagnosis of exclusion" (9), often without any effort to exclude other diagnoses. "Virus-like" symptoms, such as fever, myalgia, and arthralgia, are common in early Lyme disease, although respiratory and gastrointestinal symptoms are uncommon. Nonetheless, "flu-like" symptoms are diagnosed as Lyme disease and are another example of imprecision; patients with acute viral syndromes years into the course of long-standing clinical problems are said to have the "flu-like" symptoms of Lyme disease.

"SYMPTOMS COMPATIBLE WITH LYME DISEASE" AND THE MISUSE OF SEROLOGIC TESTING

A patient with "symptoms compatible with Lyme disease," absent physical findings, may receive a diagnosis of Lyme disease because of positive results on "Lyme disease tests" or "Lyme serologies." These tests measure antibodies binding *B. burgdorferi* in vitro, nothing more. The antibodies *may* be a marker of exposure, but they do not document current infection and may indicate a false-positive result. The intrinsic degeneracy of the humoral immune response assures that antibodies against other organisms may bind in such tests. Thus, a positive result on serology does not prove *B. burgdorferi* exposure. Bayesian theory predicts the clinical utility of testing—minimal positive predictive value if a priori likelihood was low (9). Serologic tests were developed as an adjunct to clinical diagnosis (31), and a positive test result increases a priori likelihood. However, a weakly positive test result is often the sole "evidence" favoring Lyme disease. "Lyme disease test" and "Lyme serologies" are misleading terms, suggesting the incorrect but seemingly logical conclusion that a positive result diagnoses Lyme disease. There is no such thing as a "Lyme disease test" (8, 9, 31).

The second test in the two-tiered serologic approach is immunoblot. Antibodies to individual proteins ("bands") are assigned an approximate molecular mass in kilodaltons. The CDC recommendation is that positive or equivocal results on enzyme-linked immunosorbent assays be supplemented by immunoblot (31) because the latter is more specific and the former, a first-level test, is intended to be more sensitive. Criteria were established for interpretation of results on immunoblot—IgM assays for early disease and IgG for later disease (31).

The "clinical diagnosis" of Lyme disease is often incorrectly secured by positive serologic results with negative findings on immunoblot (a "biologic false-positive" test result, borrowing again from syphilis). If a priori belief in the diagnosis is sufficient, a negative test result is dismissed—after all, "we all know how inaccurate the tests are." Regardless of results, the "clinical diagnosis" stands. Serologies are useful; their major limitation is the knowledge of the clinician who orders them and interprets the results.

Misinterpretation of immunoblot was common with earlier assays, often because of the assignment of "positive" or "negative" results to each "band," with the "positive" band being misread as a positive immunoblot finding. New reportage suggests referring to small print at the bottom of the report and understanding that IgM and IgG criteria should be used for early and later infection, respectively. Isolated IgM reactivity does not indicate chronic Lyme disease—IgG reactivity should have emerged. IgM reactivity occurs in *early* infection but has been misinterpreted as indicating *active* infection. Seroreactivity, even with IgM, can persist long after cure—persisting seroreactivity is not evidence of ongoing infection (27, 32–34). Nonetheless, a single reactive band has been misinterpreted as indicating infection, and "chronic Lyme disease" has been misdiagnosed because of seroreactivity persisting after therapy.

THE PERMANENCE OF A LYME DISEASE DIAGNOSIS

Even if proof of diagnosis at inception is tenuous, subsequent physicians may accept the previous Lyme disease diagnosis, often without independent scrutiny, as if it were proven beyond doubt. The diagnosis becomes permanent (35), all future findings perforce Lyme disease-related, making post hoc ergo propter hoc ("after this, therefore, because of this") logic all the more fallacious since the initial diagnosis was incorrect. The neologism "chronic Lyme disease" is the most damaging term in this developing imprecise lexicon. The diagnosis becomes life-long, a misdiagnosis causing missed diagnoses; the explanation for the patient's problems is never identified, and the accepted misdiagnosis prevents further search. Musculoskeletal pain is "Lyme arthritis,"and cognitive dysfunction is "central nervous system disease."

Many patients cleave to "chronic Lyme disease" despite lack of response, expense, and significant toxicities (36). It is human nature to seek explanations. The fear of the unknown can be greater than the fear of even incurable chronic disease. Anxiety and fear drive the pursuit of diagnosis, testing, and treatment (37). Achieving a diagnosis, even one of incurable "chronic Lyme disease," may offer patients with chronic symptoms comfort and assurance.

THE EFFECTS OF ANTIBIOTICS ON "CHRONIC LYME DISEASE"

Symptoms that develop or worsen during antibiotic therapy are "Herxheimer-like" reactions. A Jarisch–Herxheimer reaction occurs in about 10% of patients within days of initial antibiotic administration and not after subsequent courses. Worsening of symptoms without objective findings with a periodicity of about 28 days (the organism's "natural rhythm") is neither a Jarisch–Herxheimer nor a Herxheimer-like reaction; neither Jarisch nor Herxheimer would recognize these as what they described (36).

If symptoms persist despite antibiotic use, there may be ongoing infection (36) requiring further treatment. This could include months or years of oral or intrave-

Table 2. **Lyme Disease Terminology: Present and Proposed**

Current Term	Proposed Substitution	Why the Change Is Needed
Clinical diagnosis	No change	It is and always will be a clinical diagnosis, but the diagnosis must be based on explicit evidence of the disease and never made as a "diagnosis of exclusion."
Diagnostic tests	Sero-confirmatory tests	Testing should never be used as the sole basis for the diagnosis of Lyme disease. A positive test result is not diagnostic; it merely increases the likelihood of the diagnosis previously based on explicit clinical evidence. "Vide supra"–Bayes theorem: if the clinical suspicion of Lyme disease is low, a positive test result does not make the diagnosis. In a case with a high a priori likelihood of Lyme disease, a positive test result can do no more than confirm the clinician's conclusion of a reasonably high likelihood of disease. Some argue persuasively that even "sero-confirmatory" is too strong a term—perhaps more accurate (but less euphonious) would be "sero-suggestive."
Lyme disease test	Anti–*Borrelia burgdorferi* antibody test	The test does not diagnose Lyme disease. The test merely identifies antibodies binding to *Borrelia burgdorferi* in vitro, antibodies possibly not made in an immune response to *B. burgdorferi* in the first place. So, why not call it what it really is?
Flu-like symptoms	Viral syndrome	Influenza often includes prominent pulmonary symptoms that are relatively rare in Lyme disease. Likewise, gastrointestinal symptoms are not prominent in early Lyme disease.
Chronic Lyme disease	–*	This term is of no proven value in the management of patients with established Lyme disease. Until scientific studies prove that chronic *B. burgdorferi* infection exists, especially following what would otherwise seem to be adequate antibiotic therapy, this term should not be used. This is in contrast to the term "post–Lyme disease syndrome," which appears to describe a real clinical entity not associated with ongoing *B. burgdorferi* infection.
Lyme disease	Lyme borreliosis	The term "Lyme disease" means so many different things to different people at this point that a new name emphasizing the underlying infection with *B. burgdorferi* might help shift the focus back where it belongs—to a multisystem inflammatory disease due to an infection with *B. burgdorferi*.
Symptoms of Lyme disease	–*	The symptoms seen in patients with Lyme disease are not unique for any of the clinical manifestations of the diseases, but most emphatically for early disease. Patients with early Lyme disease may have fever, myalgias, and arthralgias, suggesting a "viral syndrome," but such symptoms are not unique to or specific for this infection; such symptoms in the summer or early fall are probably related to a viral infection. Thus this term is rendered meaningless by its lack of specificity.
Symptoms compatible with Lyme disease	–*	This term is also rendered useless by its imprecision and bias. So many of the symptoms of Lyme disease are found in other diseases that there is no way to directly ascribe them to Lyme disease—nearly all nonspecific symptoms thereby are "compatible" with Lyme disease. "Symptoms compatible with Lyme disease" takes in the entire spectrum of medicine and is a needlessly biased and suggestive term that should be abandoned.
"Lyme literate"	–*	A neologism, coined by lay support groups, that seems to identify clinicians subscribing to the empiricists' approach. "Listening to the patient" is not an attribute unique to clinicians in this group, just as all "Lyme literate" practitioners do not eschew the development of an appropriate and thorough differential diagnosis in order to make Lyme disease a "diagnosis of exclusion."

* The absence of a proposed replacement suggests that this term should be deleted from use for the reasons noted.

nous antibiotics, or combination antibiotics, occasionally including agents that are inactive against *B. burgdorferi* (for example, atovaquone). With few exceptions, such as *Tropheryma whippelii* and mycobacteria, no bacteria necessitate long-term antibiotic therapy as is used for "chronic Lyme disease."

Long-term antibiotic therapy, however, is needed because *B. burgdorferi* becomes dormant or hides within cells (38–41); these interactions protect the organism from antibiotics (42) (in vitro phenomena not documented in vivo) so that organisms are not responsive. Empiricists call proven regimens "conservative therapy" (1–3, 20, 22), a pejorative term suggesting incompetence of rationalist approaches. Transient response indicates a need for more treatment; many antibiotics have nonantimicrobial effects (43). Inadequacy of treatment is the only explanation for lack of response; the nonexistence of infection is not considered. A recent National Institutes of Health–funded trial showed that 3 months of antibiotics for "chronic Lyme disease" was ineffective (44); unfortunately, empiricist criticism will probably dismiss the results.

Peer-reviewed experience from academic referral centers indicates that most patients unresponsive to antibiotics do not have Lyme disease (35, 45–48). Some never had it; others were cured of *B. burgdorferi* infection. Symptoms following Lyme disease should not necessarily be ascribed to preceding *B. burgdorferi* infection. Such patients should be evaluated for objective evidence of inflammation and organ damage and evidence of current infection; the post hoc ergo propter hoc approach has often proven hazardous. There are "post-Lyme disease syndromes," such as fibromyalgia and depression, that do not respond to antibiotics (35, 44–47); fibromyalgia following Lyme disease is not due to ongoing infection. Objective neurologic deficits may be due to irreversible brain damage from Lyme disease, but if previous therapy was adequate, antibiotics are unlikely to be useful. Anxiety elicited by fears of incurable "chronic Lyme disease" does not respond to antibiotics. Above all, one must individualize the approach to the patient.

THE EFFECTS OF "CHRONIC LYME DISEASE" ON THE PATIENT

Long-term antibiotic therapy is not without financial and physical costs, such as bone marrow toxicity, central line sepsis (49, 50), or even death (51). Hidden in this epidemic of chronic disease and debility is the psychological cost of accepting a disease as a permanent part of yourself, that you will never be cured, that the disease will be with you forever, no matter how powerful the drugs or how aggressively they are given. Assumption of the "sick role" leaves an invisible scar that may be the most devastating effect of "chronic Lyme disease" (8).

PROPOSALS FOR CHANGES IN TERMINOLOGY—REDUCING BIAS IN THE LANGUAGE

Twenty-five years after the description of Lyme disease we have come far: clinical features are well described, accurate tests support the diagnosis, effective therapy is available, and there is an effective vaccine. It is time to reflect on the jargon that contributes to misdiagnosis and mistreatment. **Table 2** highlights some of the more troublesome terms and proposed substitutions. Use of less suggestive, accurate, unbiased terminology will help us focus on Lyme disease and take proper care of our patients, many of whom have been ill-served by cant and rhetoric. Those convinced that "chronic Lyme disease" is real, that long-term antibiotics are needed, will not be easily deterred by this analysis. However, the unbiased may use this analysis to carefully inspect the rationalist and empiricist approaches and decide which fulfills our sacred responsibility to "do no harm." Issues considered in this review may help physicians deal rationally with future clinical controversies.

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MEDICAL WRITINGS

BOOK NOTES

Structured abstracts of information on newly published books, computer programs, selected Web sites, and other material are provided in this portion of Medical Writings. "Order phone" numbers can be used to place orders directly with publishers.

The Breast Cancer Wars

Lerner BH. 400 pages. New York: Oxford Univ Pr; 2001. $30.00. ISBN 0195142616. Order phone 800-451-7556.

Field of medicine: Medical history, public health, and oncology.

Format: Hardcover book.

Audience: Oncologists, oncologic surgeons, cancer control scientists, and readers interested in the social history of medical and public health trends.

Purpose: To review the history of breast cancer treatment and control in the United States over the past century, with focus on tensions between medical, policymaking, and public perspectives on cancer control strategies.

Content: The 13 chapters proceed in chronologic order, beginning with a detailed history of the development and widespread adoption of the Halstead radical mastectomy in the late 1800s. The author then discusses the rise of the major cancer control agencies in the United States in the 1950s—including the American Cancer Society and the National Cancer Institute—and public campaigns for early cancer detection. The author discusses the ongoing contribution of patient and women's activism in breast cancer, framed in its historic context across the second half of the century. Final chapters cover current controversies in breast cancer control, including high-dose chemotherapy and age-group screening recommendations.

Highlights: Excellent use of source material, including historic documents (such as advertising) and extensive personal interviews and biographies. The early history of the American Cancer Society and the many patients with breast cancer who became advocates is especially compelling.

Limitations: Issues such as primary risk for breast cancer and the public controversy over risk factors such as childbearing, diet, and oral contraceptives, as well as environmental risks, could have received more attention. The book appears to overlook the field of medical oncology, and casts the history of breast cancer as a battle among surgeons, women, and statisticians. Although the Halstead radical mastectomy is one of the most significant controversies, it is by no means the only debate. In addition, some discussion of disease burden at a population level, including changes in incidence and mortality among age and ethnic groups, would have been helpful. Paradoxically, with its individual-level focus, the book reinforces the very 1950's image of breast cancer that it attempts to debunk—that of the patient as housewife and her male surgeon.

Related reading: Leopold's *A Darker Ribbon: Breast Cancer, Women, and Their Doctors in the Twentieth Century* (Beacon Pr, 1999) highlights historical correspondence between two women and the surgeons treating them for breast cancer.

Reviewer: Ann C. Klassen, PhD, Johns Hopkins School of Public Health, Baltimore, Maryland.

Management of Chronic Viral Hepatitis

Gordon SC, ed. 380 pages. New York: Marcel Dekker; 2001. $150.00. ISBN 0824705823. Order phone 800-228-1160.

Field of medicine: Hepatology.

Format: Hardcover book.

Audience: Primary care physicians, generalists, gastroenterology fellows, medical residents, and medical students.

Purpose: To provide a comprehensive review of the current diagnostic and treatment options for chronic hepatitis B, C, and D.

Content: This book is essentially divided into three sections, each of which discusses recent advances in the management of chronic hepatitis. The first two chapters describe the virologic testing involved in the diagnosis of both acute and chronic hepatitis B and C. Four chapters examine current and future treatment options for a variety of patients with chronic hepatitis B (post-transplantation, co-infected with HIV, and co-infected with hepatitis D). The other seven chapters focus on the management of various types of patients with hepatitis C (including post-transplantation, HIV co-infection, and patients with normal aminotranferase levels).

Highlights: Each chapter begins with a clinical case presentation that characterizes the management issues being discussed. The authors continue to refer to the clinical vignette during the discussion. The chapters are well written and easy to read. A bibliography containing a wealth of references concludes each chapter. The charts and figures spread throughout the book neatly summarize important information.

Limitations: Most case presentations do not include normal laboratory values, which would be helpful for medical personnel lacking experience with patients who have hepatologic disorders. The chapters on future treatments for hepatitis B and C may be too complicated for much of the targeted audience.

Related reading: Textbooks such as Schiff and colleagues' *Schiff's Diseases of the Liver* (Lippincott Williams & Wilkins, 1998) and Zakim and Boyer's *Hepatology: A Textbook of Liver Disease* (WB Saunders, 1996) are more comprehensive. However, *Management of Chronic Viral Hepatitis* is an important addition since it provides a current and easy-to-use reference for the practicing physician.

Reviewer: Kenneth D. Rothstein, MD, Division of Hepatology, Center for Liver Disease, Albert Einstein Medical Center, Philadelphia, Pennsylvania.

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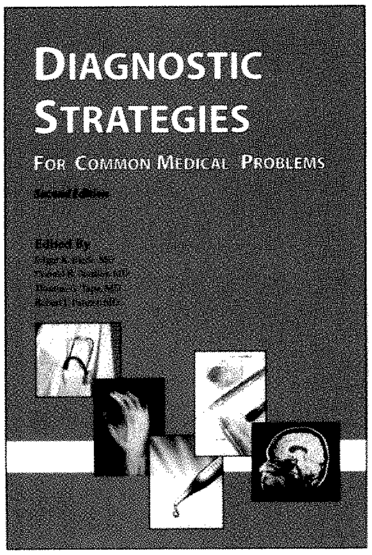

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The patient is 175 cm (69 in) tall and weighs 50 kg (110 lb). Blood pressure is 115/70 mm Hg, pulse is 96/min, and temperature is 36.9 °C (98.4 °F). The skin shows a truncal and proximal extremity rash consisting of grouped vesicles on an erythematous base. There is also evidence of excoriation. The remainder of the physical examination, including pelvic and rectal examination, is otherwise normal, and stool is negative for occult blood. The neurologic examination is normal.

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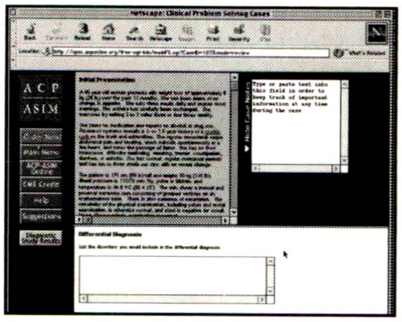

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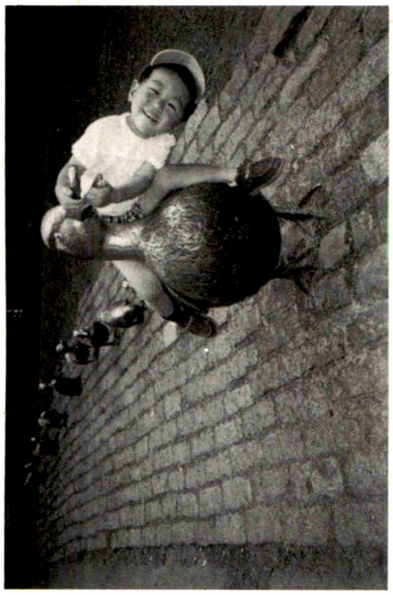

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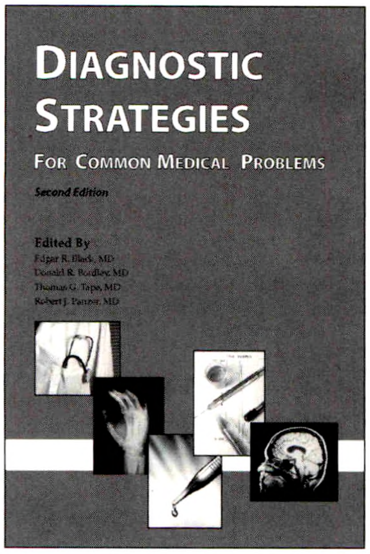

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R.P. Smith, R.T. Schoen, D.W. Rahn, V.K. Sikand, J. Nowakowski, D.L. Parenti, M.S. Holman, D.H. Persing, and A.C. Steere

In major endemic areas in the United States, Lyme disease commonly presents as erythema migrans with homogeneous or central redness and nonspecific flu-like symptoms. Clinical outcome is excellent if antibiotic therapy is administered soon after symptom onset.

Efficacy of Resident Training in Smoking Cessation: A Randomized, Controlled Trial of a Program Based on Application of Behavioral Theory and Practice with Standardized Patients 429

J. Cornuz, J.-P. Humair, L. Seematter, R. Stoianov, G. van Melle, H. Stalder, and A. Pécoud

A smoking cessation training program that was based on behavioral theory and practice with standardized patients significantly increased the quality of physicians' counseling, smokers' motivation to quit, and rates of smoking abstinence at 1 year.

J-Shaped Relationship between Blood Pressure and Mortality in Hypertensive Patients: New Insights from a Meta-Analysis of Individual-Patient Data 438

F. Boutitie, F. Gueyffier, S. Pocock, R. Fagard, and J.P. Boissel, for the INDANA Project Steering Committee

Several studies in hypertensive patients receiving treatment have described the relationship between blood pressure and mortality as J-shaped, with an increased risk for events in patients with low blood pressure. This study found that the increased risk for events in patients with low blood pressure was not related to antihypertensive treatment and was not specific to blood pressure–related events. Poor health conditions leading to low blood pressure and an increased risk for death probably explain the J-shaped curve.

BRIEF COMMUNICATION

Mixed Hepatocellular–Cholestatic Liver Injury after Pioglitazone Therapy 449

L.D. May, J.H. Lefkowitch, M.T. Kram, and D.E. Rubin

As suggested by the patient described in this report, patients receiving pioglitazone may develop serious liver injury and should be observed for evidence of hepatitis.

UPDATE

Update in Women's Health 453

N.C. Dolan, K. Freund, and J. Walsh

This Update discusses issues affecting women of reproductive age, breast cancer treatment, hormone replacement therapy, osteoporosis, cancer screening, and sexual dysfunction.

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Long-Term Medical Care of Testicular Cancer Survivors 463

D.J. Vaughn, G.A. Gignac, and A.T. Meadows

This case-based discussion focuses on the primary care physician's evaluation and management of a long-term survivor of testicular cancer who was previously treated with surgery and chemotherapy.

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Deconstructing the Placebo Effect and Finding the Meaning Response 471

D.E. Moerman and W.B. Jonas

The authors provide a new perspective with which to understand what for a half-century has been known as the "placebo effect." As currently used, the concept includes much that has nothing to do with placebos, confusing the most interesting and important aspects of the phenomenon. The authors propose a new way to understand those aspects of medical care, plus a broad range of additional human experiences, by focusing on the idea of "meaning," to which sick people often respond.

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Recognition and Treatment of Erythema Migrans: Are We Off Target? 477

R.B. Nadelman and G.P. Wormser

In this issue, Smith and colleagues describe the clinical manifestations of illness and outcome in a group of U.S. patients with erythema migrans and laboratory evidence of *Borrelia burgdorferi* infection. Their findings suggest that objective review of the information from clinical studies should change the way we think about diagnosing and treating early Lyme disease.

"Did This Drug Cause My Patient's Hepatitis?" and Related Questions 480

D.W. Nierenberg

What should the busy internist do when his or her patient, while taking several medications, suddenly develops a new clinical problem, such as hepatitis? Is the acute hepatitis drug related? If so, which drug is to blame? In this issue, May and colleagues discuss liver injury attributed to use of pioglitazone.

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On Growing Old 484

M. Lundberg

What happened to that skinny kid—the one so skinny her ribs could be counted just by looking? Today, she is a twittery, purse-clutching, cane-wielding, pill-popping little old lady living alone.

ON BEING A DOCTOR

An Examination of Conscience 486

M.S. Wheby

Petty illness, trifling fever, transient myalgias had led me to something more: a desperate need to hold on to that something that is the very essence of doctoring.

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Annals of Internal Medicine | ARTICLE

Clinical Characteristics and Treatment Outcome of Early Lyme Disease in Patients with Microbiologically Confirmed Erythema Migrans

Robert P. Smith, MD, MPH; Robert T. Schoen, MD; Daniel W. Rahn, MD; Vijay K. Sikand, MD; John Nowakowski, MD; Dennis L. Parenti, MD; Mary S. Holman, BA; David H. Persing, MD, PhD; and Allen C. Steere, MD

Background: Lyme disease has a wide spectrum of clinical manifestations. Diagnosis is usually based on the clinical and serologic picture rather than on microbiological confirmation.

Objective: To examine the clinical presentation and treatment outcome of early Lyme disease in patients with microbiologically confirmed erythema migrans.

Design: Observational cohort study.

Setting: 31 university-based or clinician-practice sites in 10 endemic states.

Participants: 10 936 participants enrolled in a phase III trial of Lyme disease vaccine; 118 participants had erythema migrans in which *Borrelia burgdorferi* was detected by culture or polymerase chain reaction.

Measurements: Clinical characteristics and treatment outcome were noted. Skin biopsies of erythema migrans were performed for culture and detection of *B. burgdorferi* by polymerase chain reaction; serologic responses were determined by Western blot.

Results: The 118 patients with microbiologically confirmed erythema migrans presented a median of 3 days after symptom onset. Early erythema migrans commonly had homogeneous or central redness rather than a peripheral erythema with partial central clearing. The most common associated symptoms were low-grade fever, headache, neck stiffness, arthralgia, myalgia, or fatigue. By convalescence, 65% of patients had positive IgM or IgG antibody responses to *B. burgdorferi*. Most patients responded promptly to antibiotic treatment.

Conclusions: In major endemic areas in the United States, Lyme disease commonly presents as erythema migrans with homogeneous or central redness and nonspecific flu-like symptoms. Clinical outcome is excellent if antibiotic therapy is administered soon after symptom onset.

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Lyme disease in the United States is caused by the tick-transmitted spirochete *Borrelia burgdorferi* sensu stricto (1). This infection is the most common vector-borne disease in the country (2). The illness usually presents with localized infection of the skin, erythema migrans, which is often followed days to a few weeks later by dissemination of the spirochete to multiple sites, particularly to other skin sites, the nervous system, the heart, or the joints (3). *Borrelia burgdorferi* has been cultured readily from skin biopsy samples of erythema migrans early in the illness (4, 5), but later culture from other sites has been difficult. As a substitute for culture, *B. burgdorferi* DNA may be detected by polymerase chain reaction (PCR) in most patients with erythema migrans (6, 7) and in the joint fluid of patients with Lyme arthritis (8, 9). However, PCR has had low sensitivity in samples from other sites, including cerebrospinal fluid and blood. Serodiagnosis is not sensitive during the first several weeks of infection, but patients often seroconvert during convalescence (10).

The initial clinical series of patients with early Lyme disease (11) was described before identification of the causative agent. Researchers used clinical criteria for study entry, particularly the classic appearance of erythema migrans, a slowly expanding erythema with partial central clearing. In that series of 314 patients, most had systemic symptoms and nearly half also had multiple annular erythemas, suggesting dissemination of the spirochete to multiple sites. In a subsequent study, 79 patients from Westchester County, New York, with early Lyme disease had erythema migrans from which *B. burgdorferi* was cultured (12). Most of the patients in this series, who were often seen earlier than those in the original study, had systemic symptoms, but only 18% had multiple erythemas.

In Europe, where erythema migrans more often results from infection with *B. afzelii* or *B. garinii* rather than *B. burgdorferi* sensu stricto, inflammation of erythema migrans is less intense and migration is slower; in addition, patients generally have fewer systemic symp-

Context

Lyme disease is the most common vector-borne disease in the United States.

The traditional clinical presentation, an expanding erythematous rash with partial central clearing, sometimes accompanied by systemic symptoms, was described in patients who usually had clinically manifest Lyme disease for several days.

Contribution

This study describes 118 patients who acquired Lyme disease while under surveillance in a vaccine trial. Fifty-nine percent of rashes were homogeneous lesions, 32% had dense central erythema, and only 9% had classic central clearing. Signs and symptoms usually resolved within 3 weeks of antibiotic treatment.

Implications

Early Lyme disease may present with homogeneous or dense central erythematous lesions rather than classic erythema migrans. With antibiotic treatment, the prognosis is excellent.

—The Editors

toms (13). In the southeastern United States, patients have been reported to have erythema migrans–like skin lesions, but laboratory evidence of *B. burgdorferi* infection has been lacking. This suggests that another agent, perhaps even from the *Borrelia* genus, may cause the infection in this geographic area (14–16). Moreover, the same tick that transmits the Lyme disease agent may transmit other infectious agents, including the agent of human granulocytic ehrlichiosis and *Babesia microti*, and co-infection may influence the clinical presentation of Lyme disease (17, 18). Thus, microbiological confirmation is beneficial in describing the clinical features of Lyme disease in endemic areas in the United States.

The recent phase III study of SmithKline Beecham's Lyme disease vaccine provided an exceptional opportunity to assess the clinical picture of early Lyme disease in a large cohort of patients who acquired the infection in major endemic locations throughout the United States (19). As part of the protocol, patients who had symptoms of Lyme disease were extensively evaluated for that infection. We describe the clinical presentation, serologic results, and treatment outcome of early Lyme disease in 118 patients with microbiologically confirmed cases of erythema migrans.

METHODS

Patients

A total of 10 936 participants 15 to 70 years of age were enrolled in a double-blind, placebo-controlled study of the efficacy and safety of an outer surface protein A Lyme disease vaccine (LYMErix, recombinant outer surface protein A, SmithKline Beecham [now GlaxoSmithKline], Collegeville, Pennsylvania) at 31 sites in 10 endemic states. The Human Investigations Review Committees at all participating centers approved the study protocol. The complete protocol, as well as all members of the Lyme Disease Vaccine Study Group, have been reported elsewhere (19).

Briefly, study participants received a packet with information about Lyme disease. Participants were requested to report promptly to their clinician-investigator any symptoms that suggested infection, including onset of a new rash or flu-like illness (without predominant respiratory or gastrointestinal symptoms), arthralgias or arthritis, facial palsy, radiculopathy, or syncope. All participants who were thought to have possible Lyme disease underwent a focused history, physical examination, and laboratory testing. All clinical data were entered on an electronic data form for central analysis. Antibiotic treatment was prescribed according to recommended guidelines (20), but the actual antibiotic and the duration of treatment were at the discretion of the investigator or the patient's personal physician. Of the 10 936 participants, 146 met study criteria for definite Lyme disease and 118 had an acute illness with culture-proven or PCR-confirmed erythema migrans. Two clinicians independently reviewed photographs of erythema migrans from case-patients.

Laboratory Methods

Serologic testing was done at the New England Medical Center exclusively by Western blot (MarDx, San Diego, California), since the standard enzyme-linked immunosorbent assay would be expected to yield positive results in patients vaccinated with outer surface protein A (21). A baseline sample was obtained at study entry, and acute and convalescent samples were obtained when the patient had symptoms suggestive of Lyme disease. The diagnosis of Lyme disease was serologically supported by IgM or IgG seroconversion, or both, between baseline and the acute phase of the illness or between the acute and convalescent phases of the illness. Samples from the same participant were always tested together in the same assay. Western blot results were interpreted according to the criteria of the Centers for Disease Control and Prevention and of the Association of State and Territorial Public Health Laboratory Directors (22). On Western blot, outer surface protein A antibodies bind to a 31-kilodalton band; this is not included in the Centers for Disease Control and Prevention criteria.

Following local anesthesia, skin biopsy specimens from erythema migrans were obtained by using 2-mm punch biopsy. Half of each sample was placed directly into a 15-mL tube of Barbour–Stoenner–Kelly medium (BSK-H medium, Sigma-Aldrich, St. Louis, Missouri) with ciprofloxacin (0.4 μg/mL) and rifampin (40 μg/mL); the other half was placed in a 2-mL polypropylene plastic tube for PCR testing. Specimens were shipped the same day by Federal Express to New England Medical Center. On arrival at the laboratory, half of the medium was replaced with fresh medium. Skin samples for culture were placed in an incubator at 33 °C and were examined weekly for 1 month by darkfield microscopy for motile spirochetes. Polymerase chain reaction assays of skin biopsy samples were performed as described elsewhere (8).

Role of the Funding Source

SmithKline Beecham provided data and gave the authors permission to review them, compile them, and independently present results. Dr. Parenti was employed as a research physician with SmithKline Beecham during the early phases of the study.

RESULTS

During the 20-month study period, which covered two summers of Lyme disease transmission, 1917 of the 10 936 study participants were evaluated for possible Lyme disease (19). Of the 1917 patients, 146 (7.6%) met study criteria for definite Lyme disease, and 118 (6.2%) had microbiological confirmation of this infection by culture or PCR testing of erythema migrans. The mean age of these 118 patients was 51 years (range, 17 to 71 years); 53% were men, and 47% were women. Forty-seven percent were from New England, 51% were from mid-Atlantic states, and 2% were from Wisconsin, reflecting the locations of the study sites. June and July were the peak months of disease onset, which correlated with the expected peak questing period of nymphal *Ixodes scapularis* ticks. However, cases occurred from March through October, suggesting that adult ticks may also transmit the disease. Vaccine and placebo recipients did not differ in the size of erythema migrans, persistence of symptoms after treatment, and morphologic characteristics of the lesions. In addition, no clinical differences were noted in different geographic areas. Therefore, we present data from vaccine and placebo recipients and from different geographic areas together.

Characteristics of Erythema Migrans

One hundred eighteen patients had erythema migrans in which *B. burgdorferi* was detected by culture (88%); by PCR testing (72%); or, in most instances, by both methods (60%). Rashes, which were evaluated a median of 3 days after onset (range, 1 to 30 days), were a median of 10 cm in diameter (range, 5 to 37 cm) at the time of diagnosis. In this adult population, nearly half of the lesions were located on the groin, buttocks, or lower extremities and approximately one quarter were found on the shoulder, axilla, or upper arm. On the basis of photographs, which were available in 95 cases, 59% of the rashes consisted of homogeneous erythema and 32% had more intense central erythema surrounded by a paler peripheral ring (**Table 1; Figures 1, 2, and 3**). Atypical lesions, such as those with vesicular or ulcerated centers, were occasionally noted (**Figure 3**). Nine patients (7.6%) had multiple annular skin lesions, a sign of disseminated infection.

Associated Signs and Symptoms

The most common signs and symptoms associated with erythema migrans were nonspecific flu-like symptoms, including myalgia, arthralgias, fever, headache, fatigue, or neck stiffness (**Table 1**). Fever was reported in 30% of patients but was documented at office evaluation in only 6%. In addition to erythema migrans, three patients had facial palsy and two had trigeminal-nerve dysesthesias. None of the patients had arthritis or carditis.

Serologic Findings

Of the 116 patients tested serologically by Western blot, 27% had detectable IgM responses alone, 3% had IgG reactivity alone, and 4% had both IgM and IgG responses to *B. burgdorferi* in acute-phase samples. Two to 4 weeks later, 44% had IgM responses only, 10% had IgG reactivity only, and 11% had both IgM and IgG

Table 1. **Morphologic Pattern and Associated Signs and Symptoms of Erythema Migrans**

Variable	Patients, *n* (%)
Morphologic characteristics	
Predominant pattern	
Homogeneous	56 (59)
Central erythema	30 (32)
Central clearing	9 (9)
Punctum present	29 (31)
Vesicular or ulcerated	7 (7)
Blue center	2 (2)
Total	95 (100)
Signs and symptoms	
Myalgia or arthralgia	41 (35)
Fever	36 (31)
Headache	33 (28)
Fatigue	12 (10)
Stiff neck	6 (5)
Cranial neuritis (facial palsy or trigeminal paresthesia)	5 (4)
Other paresthesia	3 (2.5)
Lymphadenopathy	3 (2.5)
Nausea	3 (2.5)
Malaise	2 (2)
Back pain	2 (2)
None	51 (43)
Total	118 (100)

responses. The frequency of seropositivity in acute-phase samples increased with the duration of illness before evaluation. Seropositivity was seen in 27% of patients who had had symptoms for fewer than 7 days, 41% of those who had had symptoms for 7 to 14 days, and 88% of those who had had symptoms for more than 14 days.

Antibiotic Treatment and Outcomes

Data about antibiotic treatment were available for 115 of 118 patients (Table 2). Most patients were treated with oral doxycycline or amoxicillin for 14 to 30 days, beginning a median of 4 days after illness onset. Two patients, both presenting with erythema migrans, facial palsy, and paresthesias, were treated with intravenous ceftriaxone. Four patients received oral antibiotic treatment for fewer than 14 days, but they responded well without sequelae. Signs and symptoms usually resolved within 3 weeks after treatment.

However, in 13 patients (11%), signs or symptoms persisted for more than 30 days after treatment, and 5 patients (4%) had persistent symptoms for more than 60 days. In 3 cases, these symptoms were subjective, including fatigue, headache, or arthralgia. The other 2 patients had residual neurologic symptoms of facial numbness or weakness. During acute infection, these 13 patients had erythema migrans accompanied by fever, flu-like symptoms, or neurologic symptoms. One patient treated for erythema migrans with a 4-week course of doxycycline developed a small, transient knee effusion 11 months later. The joint was not aspirated. Results of serologic testing for Lyme disease were negative. Although Lyme arthritis was not thought to be the cause of the effusion, the patient received another 30-day course of doxycycline without recurrence of symptoms. By the end of the study, all patients had recovered completely except for one patient with persistent myalgias.

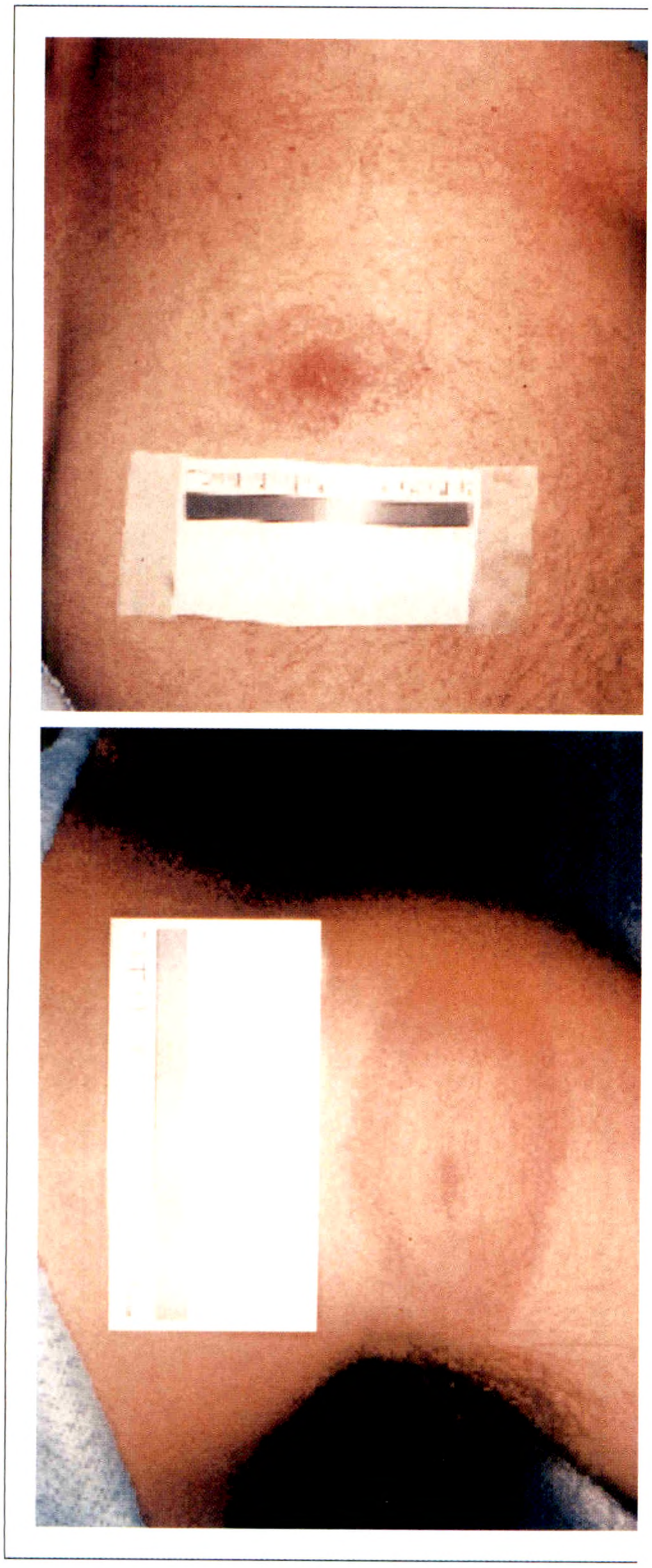
Two patients had erythema migrans twice. One developed erythema migrans in the first year and again in the second year, and the other developed erythema migrans in the summer and again in the fall of the same year. In both cases, the second lesion was in a different location from the first, and *B. burgdorferi* was cultured from both the first and second lesions. With the first lesion, both patients had only IgM responses to *B. burgdorferi.* With the second lesion, the IgG response to the spirochete rapidly expanded. Both patients responded rapidly to 2-week courses of doxycycline.

DISCUSSION

Of 118 patients who had early microbiologically confirmed Lyme disease and presented with erythema migrans, most had homogeneous erythema; approximately half had associated symptoms of low-grade fever, headache, neck stiffness, myalgia, arthralgia, or fatigue; and only a minority were initially seropositive for *B. burgdorferi.* Most patients responded promptly to recommended courses of antibiotic therapy, and most seroconverted between the acute and convalescent phases.

After a tick injects *B. burgdorferi* and an incubation period of 3 to 32 days passes, the spirochete usually multiplies locally in the skin at the site of the tick bite and then spreads gradually in the skin, resulting in erythema migrans (3). It is primarily during this period that it has been possible to culture *B. burgdorferi* from infected persons (4, 5, 12, 13, 19). (In our series, similar to others reported [6, 7, 23], PCR was slightly less effective than culture in detecting spirochetal DNA.) Within days to weeks, depending on spirochetal virulence and host factors (24), *B. burgdorferi* may then disseminate to multiple sites, particularly to other skin sites, the nervous system, the heart, or the joints (3, 11).

Figure 1. **Erythema migrans with central erythema or central clearing.**



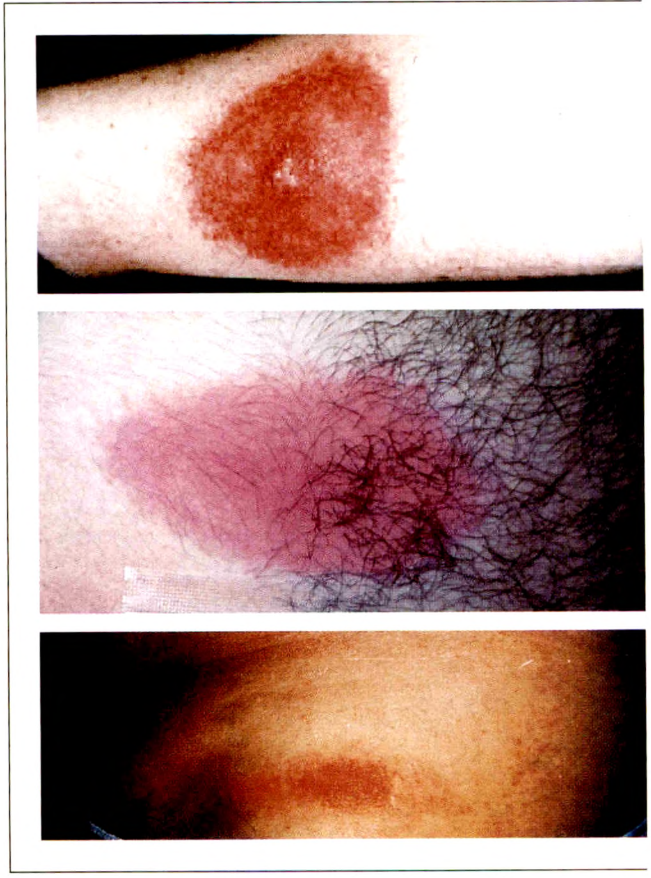
Top. Bull's-eye lesion, 7 cm in diameter, that had been present for 11 days. **Bottom.** 9-cm lesion that had been present for 18 days and exhibits marked central clearing.

Median duration of erythema migrans before evaluation and treatment was shorter in our patients than in previous series, presumably because our patients were asked to report promptly to the clinician-investigator if symptoms of possible Lyme disease developed. Thus, compared with previous reports (11, 12), lesions were smaller in our study and often homogeneous in appearance. Classic erythema migrans (a bright-red outer border with partial central clearing) had not yet evolved in most patients. Similarly, only 7% of our patients had multiple annular erythema migrans, compared with 48% of patients in the initial series (11), presumably because the spirochete had not yet disseminated in many cases. The signs and symptoms associated with erythema migrans were similar to those in previous reports but occurred in fewer patients (11, 12). Lymphadenopathy, in particular, was reported in only 2% of our patients; however, this may be due to errors in reporting since lymphadenopathy was not included in the standard clinical data sheet. Facial palsy, noted in three of our patients (2.5%), is a well-recognized manifestation of Lyme disease and may be the presenting sign of the illness (25, 26). Other cranial nerves may also be affected (27); dysesthesias in the distribution of the trigeminal nerve were also noted in two study patients (1.7%).

As previous studies found (10, 28–30), IgM or IgG responses to *B. burgdorferi* were found in 34% of acute-phase samples and in 65% of convalescent-phase samples on Western blot. Specific antibody responses are generated in peripheral lymph nodes, a process that requires at least several days. Thus, most patients with early Lyme disease, particularly if *B. burgdorferi* is still localized to the skin, do not yet have a humoral immune response to the spirochete. However, antigen processing and spirochetal killing continue for some time after antibiotic treatment begins, and a positive response can thus more often be detected in convalescent-phase samples. Although serologic testing may not be necessary in patients with classic erythema migrans (31), it is important to test both acute- and convalescent-phase serum samples if laboratory support of the diagnosis is needed.

In our study, most patients received recommended 14- to 30-day courses of doxycycline or amoxicillin and had prompt resolution of symptoms. Thirteen patients

Figure 2. **Predominantly homogeneous patterns in erythema migrans.**



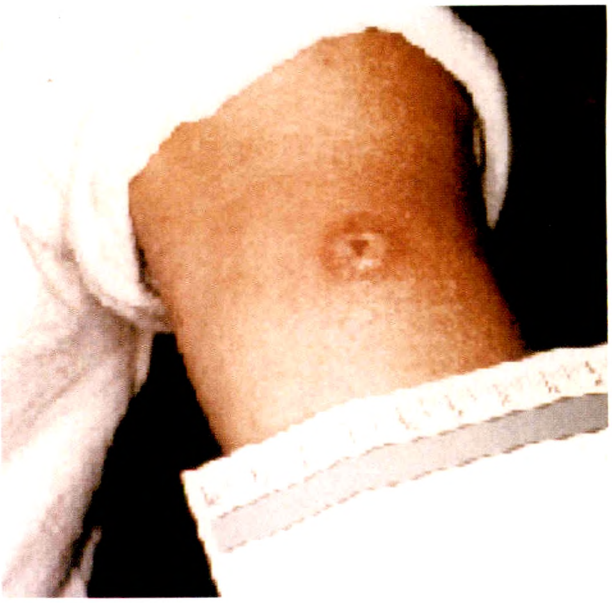
Top. Lesion, 10 cm in diameter, that had been present for 7 days; it has slight vesiculation in the center. **Middle.** Homogeneous lesion, 11 cm in diameter, that had been present for 7 days; no target formation or central clearing is seen. **Bottom.** 7-cm lesion, present for 12 days, that has some degree of central erythema.

(11%) had persistent fatigue or arthralgia for weeks after treatment. Similarly, in previous studies, oral antibiotic treatment of early Lyme disease was rapidly effective in more than 90% of patients (32–37); 5% to 10% of patients had arthralgias or fatigue for more than 1 month after treatment, and objective late manifestations occurred in fewer than 5% (32–37). One patient still had myalgias at the conclusion of our study. Fatigue, myalgias, or neurocognitive symptoms that persist after treatment for Lyme disease are sometimes called post–Lyme disease syndrome (38). This syndrome does not seem to respond to antibiotic therapy (39).

Two of our patients developed erythema migrans a second time, one during the fall of the same year and the other during the next summer. Although we lack formal proof, we believe reinfection with the Lyme disease agent caused these second cases. Both patients responded well to initial treatment and had no symptoms in the intervening period; the second cases of erythema migrans occurred at different sites, and the IgG response expanded rapidly, suggesting an anamnestic response. Reinfection has been reported previously, but not in the same or consecutive years (40, 41). Reinfection has not been documented in patients with late Lyme disease, particularly those with Lyme arthritis, who have an expanded antibody response to the spirochete.

Our study has several limitations. First, because the primary purpose of data collection was testing vaccine safety and efficacy, clinical information was collected in a standard format by multiple investigators. Thus, some details of the clinical picture, such as the frequency of tick bite, were not readily available. Second, because the study sample was primed to report to the clinician-investigator as soon as possible symptoms of Lyme disease appeared, this study gives a clinical picture only of early Lyme disease, often in the first days of symptoms. Since microbiological confirmation of early Lyme dis-

Figure 3. **Central vesiculation of erythema migrans.**



An area of intense vesiculation can be seen at the center of this 10-cm lesion, which had been present for 5 days.

Table 2. **Antibiotic Treatment**

Antibiotic	Patients	Dosage (Cases)	Median Duration of Treatment (Range)
	n (%)	*mg/d (n)*	*d*
Doxycycline	81 (70)	200 (78) 100 (2) 300 (1)	22 (8–43)*
Amoxicillin	30 (26)	1500 (22) 3000 (3) 1000 (2) Other (3)	30 (11–38)
Intravenous ceftriaxone	2 (2)	2000 (2)	22
Amoxicillin and clavulanate	1 (1)	1500 (1)	13
Cefuroxime axetil	1 (1)	1000 (1)	22

* One patient was given amoxicillin after 8 days of doxycycline.

ease is primarily possible in patients with erythema migrans, this case series includes only patients with that manifestation. Finally, the study physicians followed recommended guidelines for Lyme disease treatment, but the type and duration of therapy were at the discretion of the treating physician. Thus, results of various regimens could not be compared.

In summary, this study gives an overview of microbiologically confirmed erythema migrans as seen in a clinical trial in endemic areas in the northeastern and north-central United States. During the first days of infection, most patients had homogeneous erythema, sometimes accompanied by nonspecific flu-like symptoms. Classic bull's-eye rashes with central clearing were infrequent. By convalescence, 2 to 4 weeks after antibiotic treatment, most patients were positive on Western blot for *B. burgdorferi*, usually of the IgM isotype. Signs and symptoms resolved promptly in most patients after standard 14- to 30-day courses of antibiotics, and almost all patients were completely well by the end of the study.

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Efficacy of Resident Training in Smoking Cessation: A Randomized, Controlled Trial of a Program Based on Application of Behavioral Theory and Practice with Standardized Patients

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Background: **New educational programs must be developed to improve physicians' skills and effectiveness in counseling patients about smoking cessation.**

Objective: **To assess the efficacy of an educational program based on behavioral theory, active learning methods, and practice with standardized patients in helping patients abstain from smoking and changing physicians' counseling practices.**

Design: **Cluster randomized, controlled trial.**

Setting: **Two general internal medicine clinics in Switzerland.**

Participants: **35 residents and 251 consecutive smoking patients.**

Intervention: **A training program administered over two half-days, during which physicians learned to provide counseling that matched smokers' motivation to quit and practiced these skills with standardized patients acting as smokers at different stages of change. The control intervention was a didactic session on management of dyslipidemia.**

Measurements: **Self-reported abstinence from smoking at 1 year of follow-up, which was validated by exhaled carbon monoxide testing at one clinic; score of overall quality of counseling based on use of 14 counseling strategies; patient willingness to quit; and daily cigarette consumption.**

Results: **At 1 year of follow-up, abstinence from smoking was significantly higher in the intervention group than in the control group (13% vs. 5%; $P = 0.005$); this corresponded to a cluster-adjusted odds ratio of 2.8 (95% CI, 1.4 to 5.5). Residents who received the study training provided better counseling than did those who received the control training (mean score, 4.0 vs. 2.7; $P = 0.002$). Smokers' willingness to quit was also higher in the intervention group (94% vs. 80%; $P = 0.007$). A nonsignificant trend toward lower daily cigarette consumption in the intervention group was observed.**

Conclusion: **A training program in smoking cessation administered to physicians that was based on behavioral theory and practice with standardized patients significantly increased the quality of physicians' counseling, smokers' motivation to quit, and rates of abstinence from smoking at 1 year.**

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Medical advice and pharmacotherapy are effective interventions in clinical practice to help patients stop smoking (1, 2). Although primary care physicians can play a key role in promoting smoking cessation to their patients who smoke (3), they miss many opportunities to advise smokers (4–7), mainly because they lack skills in counseling about smoking cessation (8). Residency training in ambulatory care is an ideal setting in which to learn the attitudes and skills of preventive medicine, including smoking cessation (9).

Training programs in smoking cessation improve the frequency and quality of smoking cessation interventions administered by physicians (10–17). However, training improved rates of smoking cessation at 6 months or 1 year in only two trials (17, 18) and had no significant effect on abstinence from smoking in most studies (10–16, 19). Most training programs mainly use didactic teaching rather than such potentially effective methods as active learning of practical skills (20, 21). A few training programs based on active learning methods effectively improve counseling skills, self-efficacy, and attitudes (22–25), but their effect on rates of smoking cessation remains unknown. Most programs did not consider smoking cessation as a process of change through successive stages that required counseling tailored to smokers' motivation to quit (26, 27). Use of such a model improves physicians' performance, but its effect on rates of smoking cessation at 1 year is unclear (11, 14, 19). New educational and conceptual approaches to improve physicians' skills and effectiveness in smoking cessation, particularly during residency training, should be developed (2, 28).

We used active learning methods to train physicians in smoking cessation interventions based on counseling

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Context

Training programs for counseling about smoking cessation have seldom shown a significant effect on sustained tobacco abstinence, possibly because most programs have used didactic teaching techniques. The effect of active learning methods on cessation rates is unknown.

Contribution

In this study, half the participating physicians were trained in the stages-of-change model and pharmacotherapy techniques. Counseling skills were practiced on standardized patients. The other half received no relevant training. One year later, patients of the trained residents showed a significantly higher smoking cessation rate than those of the untrained residents.

Implications

Training programs using active learning techniques increase the effectiveness of smoking cessation counseling.

–The Editors

that matched the patient's stage of change and appropriate use of pharmacotherapy. We conducted a cluster, randomized, controlled trial among residents in ambulatory care to assess the effectiveness of this training program on physicians' practices and patients' rate of smoking cessation.

METHODS

Design and Setting

We conducted a cluster randomized, controlled trial in two general internal medicine clinics of the university hospitals of Lausanne and Geneva, Switzerland. Both sites are public service clinics that provide adult ambulatory care in approximately 25 000 outpatient visits per year. Patients are assigned to residents who provide care at walk-in and follow-up visits.

We randomly assigned all 35 residents at both clinics to an intervention group trained in smoking cessation or a control group trained in management of dyslipidemia. An independent research assistant performed computer randomization stratified by clinic and concealed the result of randomization until 2 weeks before the intervention, when we provided residents with practical details about training sessions. The residents constitute the clusters; the unit of analysis is the patient.

We based our sample size calculation on the difference in rates of abstinence from smoking at 1 year (the primary outcome) among patients attended by trained residents and among patients attended by control residents. Using data from a previous local study and the literature (1, 11), we estimated that the 1-year cessation rate would be 4% in the control group and 15% in the intervention group. These estimates seemed realistic for our setting and relevant from clinical and public health perspectives. At an α value of 5% or less and a power of 80%, the required sample size was about 130 participants per group. In the sample size evaluation, we did not account for a potential clustering effect because the clinic statistics and previous research (11) showed that physicians cared for similar numbers of patients per month (average of 60 to 80) and that the correlation of patients within physicians would be small.

Participants

The residents were 18 women and 17 men; their median age was 31 years. Thirty-two were never-smokers or former smokers, and 3 were current smokers. All residents were at the end of postgraduate training in general internal medicine or family medicine (median duration of training, 4 years). None of them had previously received specific training in smoking cessation.

We used several strategies to minimize a change in professional behavior induced by the study among the residents (Hawthorne effect). Residents were blinded to the aim of the trial and were informed only that a survey on cardiovascular risk factors and prevention would be conducted among clinic patients. To mask our interest in smoking cessation counseling, we did not inform the residents that patients would be interviewed on smoking cessation interventions. We announced only that a training program in clinical prevention that included sessions on smoking cessation and management of dyslipidemia was being conducted. Residents who were first trained in smoking cessation attended the session on dyslipidemia 4 months later, and vice versa. The second session took place after the 3-month patient recruitment period had ended. To identify smokers and avoid revealing group assignments, we interviewed all patients, regardless of their smoking status. Patients were also blinded to the aim of the study and group allocation of their physician.

Figures 1 and 2 show the trial design and patient recruitment. Eligible patients were 16 to 75 years of age, understood French, consulted one of the outpatient clinics for a follow-up or an emergency visit, and had smoked one or more cigarettes daily during the previous week. Full-time research assistants recruited patients, checked their eligibility criteria, and asked them for written informed consent to participate in a study about preventive care. Of the 2430 consecutive patients approached, 1456 met the eligibility criteria; of these 1456 patients, 1277 agreed to be interviewed after the visit. Research assistants interviewed 790 patients after the consultation; 487 patients left before the interview. The sex distribution and mean age of noninterviewed patients did not differ from those of interviewed patients. Of the 790 interviewed patients, 251 (32%) were current regular cigarette smokers; these patients formed the final study sample.

The study protocol was approved by the ethics committees of both institutions.

Intervention

The smoking cessation training program for physicians was based on active learning of counseling skills and interventions that match patients' readiness to quit smoking (29, 30). After training, residents had to reach the following educational objectives: to systematically identify all patients who smoke; to clearly advise all smokers to quit; to assess each smoker's readiness to quit; to use applied counseling strategies and offer a brochure that matched their readiness to quit; to propose an individual smoking cessation program; to follow smokers in the short and long term; and to facilitate implementation of smoking cessation in routine practice.

The strategies that residents used to counsel patients about smoking cessation differed according to the patient's stage of change. For patients in the precontemplation stage (no intention to quit smoking in the next 6 months), residents were taught to inform patients about and sensitize them to tobacco use and cessation by personalizing the benefits of quitting and by challenging their beliefs. For smokers in the contemplation stage (intention to quit in the next 6 months but not within 30 days), physicians learned motivational strategies to balance pros and cons of smoking and discuss barriers to cessation and their solutions. Residents learned how to assist patients who were ready to quit smoking by show-

Figure 1. **Flow of the study.**

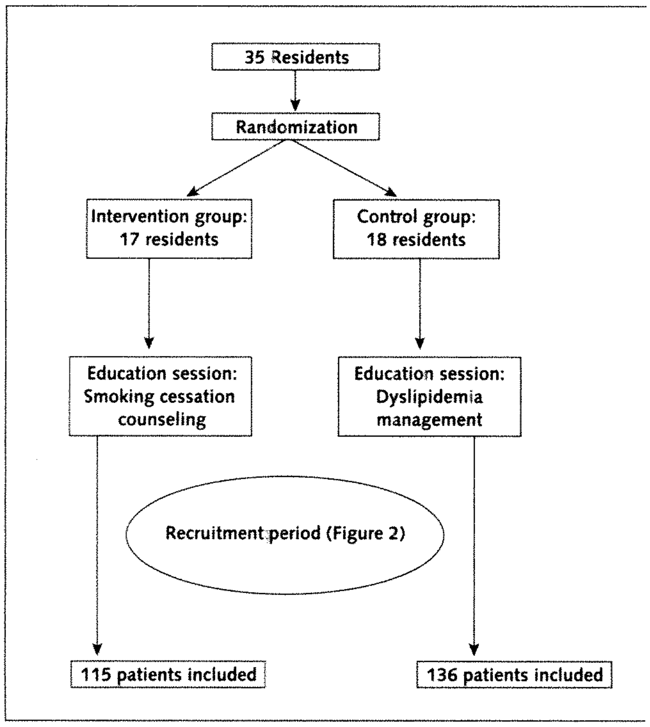
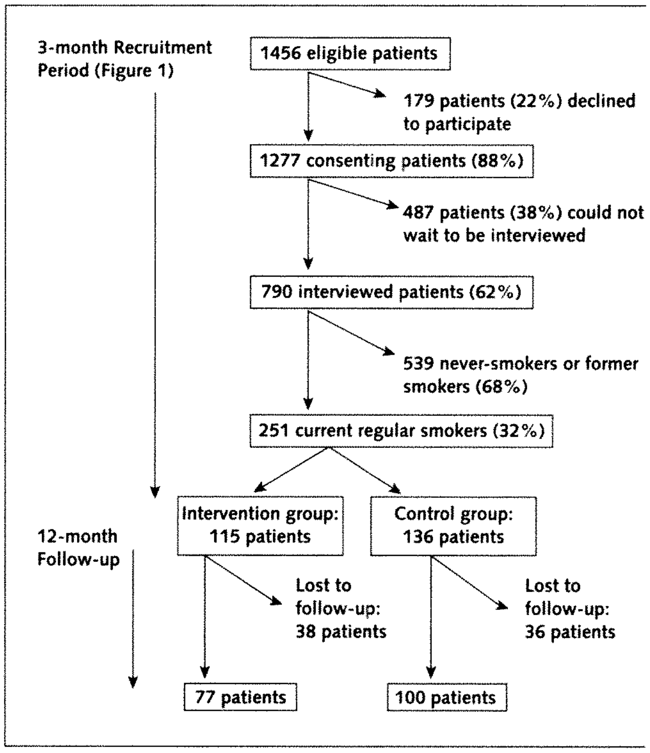

35 Residents
Randomization
Intervention group: 17 residents
Control group: 18 residents
Education session: Smoking cessation counseling
Education session: Dyslipidemia management
Recruitment period (Figure 2)
115 patients included
136 patients included

Figure 2. **Patient recruitment.**


3-month Recruitment Period (Figure 1)
1456 eligible patients
179 patients (22%) declined to participate
1277 consenting patients (88%)
487 patients (38%) could not wait to be interviewed
790 interviewed patients (62%)
539 never-smokers or former smokers (68%)
251 current regular smokers (32%)
12-month Follow-up
Intervention group: 115 patients
Control group: 136 patients
Lost to follow-up: 38 patients
Lost to follow-up: 36 patients
77 patients
100 patients

ing support, setting a quit date, prescribing nicotine replacement therapy with instructions for use, and suggesting behavioral hints to prevent relapse.

The training program comprised two half-day sessions. The first session included an analysis of three videotaped encounters with a smoking patient at successive stages of motivation, an interactive workshop with theoretical input linked to clinical cases, and role-playing between participants that was based on scenarios of smokers at various stages. The second session involved encounters with four standardized patients (two women and two men, all former smokers) who were recruited from an academic program and portrayed smokers at different stages; some had cardiovascular risk factors or smoking-related diseases. Each resident received a reference document that included algorithms for counseling and pharmacotherapy, a record sheet for smoking patients (29), and stage-matched brochures for patients that were recently developed in conjunction with an expert system program for smoking cessation (31).

Control Intervention

To ensure equal contact conditions, we chose a traditional didactic training program on management of dyslipidemia as the control intervention. This half-day course taught residents about Swiss guidelines on screening for and diagnosis and management of high blood levels of cholesterol (32). The program comprised an oral presentation of scientific evidence and several case studies in which participants applied the guidelines and interacted with the tutor.

Data Collection

Immediately after the medical visit, a research assistant interviewed patients by using a structured questionnaire. The questionnaire included sections about sociodemographic data and various cardiovascular risk factors. The last section, which was completed by current smokers, explored smoking history, motivation to quit, nicotine dependence, smoking intervention, and use of 14 specific smoking cessation strategies administered by the resident at the past three visits (Table 2). Experts in smoking cessation and primary care physicians assessed the strategies for accuracy and face validity. Reliability was not specifically determined because these questions had been extensively used and accepted for use in previous studies (11). The questionnaire was then pretested in 20 outpatients during a pilot phase. After the interview, research staff reviewed all medical records of enrolled patients to collect relevant clinical data.

At 1 year, we mailed a questionnaire to assess patients' smoking behavior, 1-week point prevalence of abstinence, and use of cessation methods. We present self-reported abstinence from smoking because biochemical validation is not necessary for a low-intensity intervention (33). Nonetheless, we validated abstinence at one clinic by having a research assistant who was blinded to group allocation measure exhaled carbon monoxide. The cut-off value was 10 parts per million, which is the recommended level to assess 24-hour abstinence from smoking.

On a questionnaire administered at baseline and 3 months after training, residents rated on a 10-point scale their self-confidence and self-perceived effectiveness in preventive medicine and smoking cessation.

Statistical Analysis

To compare baseline characteristics of patients and physicians' practices between groups, we used the chi-square or Fisher exact test for categorical data and the *t*-test or Wilcoxon rank-sum test for continuous data. To assess the overall quality of smoking cessation interventions, we devised a scoring system that ranged from 0 to 14, representing the total number of strategies used.

For abstinence from smoking, we performed an intention-to-treat analysis in which we considered smokers lost at 1 year of follow-up to be continuing smokers. Because different numbers of patients were recruited from the pool of each resident, confounding by other factors and clustering within practices could influence outcome variables and violate the assumption of independence. To measure the effect of training on the primary (abstinence from smoking at 1 year) and secondary (counseling score, willingness to quit, and daily cigarette consumption) outcomes, we performed a logistic regression with a generalized estimating equation to stratify by clinic and adjust for clustering on residents (34). This approach was used because the intervention was randomly allocated not directly to individual smokers but rather to groups of individuals or clusters (34); as a result, individuals within a cluster (that is, a physician's practice) may be more like each other than are individuals between clusters. The extent of such reduction in independence is expressed by the design effect. Because the correlations between observations were essentially equal, we used a compound symmetric covariance structure. We report the estimates of abstinence rates for the intervention and control groups and the P value calculated from the generalized estimating equation model.

Because abstinence was validated in a subsample of study participants, we used simulation to perform sensitivity analysis of the likelihood of smoking cessation. The simulation allowed us to evaluate the joint effect of false reporting and clustering on physicians. Ten thousand repetitions were performed in which the number of false reports was randomly generated among the 9 patients who quit smoking but whose abstinence was not validated (3 of 7 patients in the control group and 6 of 15 patients in the intervention group). The odds ratio of success in the intervention group versus the control group was obtained for each simulated sample by using the same analysis as that done on the actual data (that is, adjusted for clustering and stratified by clinic). The underlying rate of false reports was set at 10% in accordance with the literature (33) and was assumed to be independent of the physicians' group allocation. None of the 13 tested self-reports of smoking cessation were found to be false.

Statistical analyses were performed by using Stata statistical software (Stata Corp., College Station, Texas).

RESULTS

Resident Characteristics

At baseline, sociodemographic characteristics, professional achievements, health habits, and self-perceived effectiveness in smoking cessation counseling were similar between intervention and control residents.

Patient Characteristics

Baseline characteristics of patients in the intervention and control groups were similar in terms of age; sex; education level; type of medical visit; prevalence of cardiovascular risk factors; self-perceived health status; and smoking history, attitudes, and behavior (**Table 1**). Patients who remained in the cohort and those who dropped out after 1 year of follow-up were similar in terms of mean age (37 vs. 35 years; $P > 0.2$), proportion of men (57% vs. 64%; $P > 0.2$) and receipt of higher education (18% vs. 18%; $P > 0.2$).

Table 1. **Patient Characteristics at Baseline**

Characteristic	Intervention Group (*n* = 115)	Control Group (*n* = 136)	*P* Value
Mean age ± SD, *y*	35.1 ± 14	36.9 ± 15	>0.2
Men, %	63	57	>0.2
Attended follow-up visit, %	41	44	>0.2
Higher education, %*	18	18	>0.2
Daily consumption of ≥2 alcoholic drinks, %	9	13	>0.2
Hypertension, %†	9	7	>0.2
Diabetes, %†	1	2	>0.2
Dyslipidemia, %†	8	4	>0.2
Perceived good health, %	69	68	>0.2
Sedentary lifestyle, %‡	19	22	>0.2
Mean daily cigarette consumption ± SD, *n*	20 ± 12	20 ± 11	>0.2
Mean duration of smoking ± SD, *y*	16 ± 13	18 ± 13	>0.2
Mean age at smoking initiation ± SD, *y*	18 ± 6	18 ± 5	0.2
Previous attempts at smoking cessation, %	70	68	>0.2
Time to first cigarette after waking up, %			>0.2
<5 min	18	17	
5–30 min	20	25	
>30 min	62	58	
Stage of change, %			>0.2
Precontemplation	84	87	
Contemplation	11	6	
Preparation	5	7	

* University degree or equivalent.

† Diagnoses reported in the medical chart.

‡ Defined as less than one 20-minute session of sports activity per week.

Physician Counseling Practices

Table 2 shows the short-term effect of the training program on the frequency and content of smoking cessation counseling performed by residents. According to smokers' self-reports, trained residents used all counseling strategies more often than did control residents. In particular, they used the following strategies significantly more often: assessing motivation to quit (29% vs. 19%), offering help to quit (23% vs. 7%), discussing benefits of (21% vs. 12%) and obstacles to (16% vs. 6%) cessation, giving a brochure (14% vs. 1%), discussing strategies to prevent relapse (15% vs. 6%), and setting a quit date (8% vs. 2%). Training improved the overall quality of smoking cessation counseling, as evidenced by a higher mean score in the intervention group than in the control group (4.0 vs. 2.7; $P = 0.002$). Among smokers in the precontemplation stage, the quality of interventions also improved (mean score, 3.7 for trained residents and 2.6 for controls; $P = 0.006$). Because the design effect for all of the above results ranged from 0.9 to 1.5, the intracluster correlations were low.

Compared with control residents, trained residents expressed higher self-confidence (7.7 vs. 5.2; $P = 0.002$) and self-perceived effectiveness in smoking cessation counseling (6.8 vs. 5.4; $P = 0.09$) 3 months after training.

Smoking Cessation and Behavior among Patients

At 1 year of follow-up, 1-week smoking abstinence was significantly higher in the intervention group than in the control group (15 of 115 patients [13%; 95% CI, 7% to 21%] vs. 7 of 136 patients [5%; CI, 1% to 9%]; $P = 0.005$); these values correspond to a cluster-adjusted odds ratio of 2.8 (CI, 1.4 to 5.5) and a design effect of 0.89. The 8-percentage point difference between groups means that a trained resident needs to counsel 13 smokers to achieve 1 additional former smoker. Furthermore, in the intervention group, the proportion of smokers who were willing to quit was higher (94% [CI, 89% to 99%] vs. 80% [CI, 70% to 89%]; $P = 0.007$) and daily cigarette consumption tended to be lower (16.5 vs. 20.0; $P = 0.09$). The intervention and control groups did not significantly differ in the proportion of smokers in the precontemplation stage (84% vs. 82%; $P > 0.2$) or the proportion of smokers who moved one stage forward (13% vs. 14%, $P > 0.2$). The sex of the resident did not influence patients' cessation rates.

Table 2. **Short-Term Effect of Training in Smoking Cessation on Physicians' Practices***

Smoking Cessation Strategy Used in Physician's Intervention	Patients in Intervention Group ($n = 115$)	Patients in Control Group ($n = 136$)	*P* Value
	%		
Ask whether the patient smokes	87	78	0.13
Ask about daily cigarette consumption	82	71	0.08
Ask about the time of the first cigarette of the day	18	11	0.15
Ask whether the patient intends to stop smoking	29	19	0.05
Advise to stop smoking	39	29	0.12
Discuss the health risks of smoking	36	28	0.16
Discuss the benefits of quitting	21	12	0.05
Discuss patient's barriers to smoking cessation	16	6	0.01
Propose to help the patient quit smoking	23	7	0.003
Propose setting a quit date	8	2	0.02
Give practical advice on stopping smoking and preventing relapse	15	6	0.01
Give self-help materials	14	1	<0.001
Propose another appointment to discuss smoking cessation	7	3	0.15
Propose attending a smoking cessation program	6	3	>0.2

* The mean overall counseling score ± SD was 4.0 ± 0.3 in the intervention group and 2.7 ± 0.2 in the control group ($P = 0.001$).

Eighty-five percent and 86% of patients in the intervention and control groups, respectively, who stopped smoking reported stopping abruptly. In both groups, the main reason for quitting was health concerns (68% and 65%; $P > 0.2$).

The sensitivity analysis of smoking abstinence performed by simulation of a 10% rate of false reporting produced only 14 runs (0.14%) in which the odds ratio was significantly less than 1.0 (upper bound of CI < 1.0). The effect of potential false reports was clearly weak, and we can safely state that the adjusted odds ratio describing the effect of training on smoking abstinence is significantly larger than 1.0.

DISCUSSION

Our study shows that a physician training program in smoking cessation that was based on behavioral theory and active learning of counseling skills with standardized patients improved the frequency and quality of physician counseling and increased the 1-year rate of abstinence of smoking among outpatients. Both effects were clinically and statistically significant despite the high proportion of smokers who were not motivated to quit.

Another study showed that training physicians in smoking interventions increases the rate of smoking cessation among patients at 1 year (18). However, the intervention in that study was not specifically based on the stages-of-change model. Use of similar teaching methods and written material may account for the significant effect found in both studies.

Three reasons may explain why training was effective in our trial and not in most previous studies (10–16, 19). Participants spent more than 50% of the program in active learning methods, which are effective for medical education in general (21) and smoking cessation in particular (22–25). Other programs did not use such methods; they mainly emphasized didactic teaching, which has little influence on patient outcomes (21). The duration of our program was longer (8 hours) than other interventions (4 hours or less). Higher intensity of training may be needed to increase its efficacy, particularly for an intervention that is not adequately taught during undergraduate or postgraduate education (35, 36). Finally, we based our training program on one behavioral theory, the stages-of-change model, that enables physicians to tailor their intervention to each smoker's readiness to quit (26, 27, 37). In most trials, physicians' interventions had the same content (the four A's) regardless of patients' readiness to quit (12, 13, 15–18). Use of the stages-of-change model may help physicians to understand the process of smoking cessation and to structure their interventions.

The low frequency of a set quit date reflects the high proportion of smokers who were not ready to quit. Our findings show that an approach based on stages of change (26–28) is helpful in clinical practice, although it did not enhance smokers' progression to stages with a higher readiness to quit. Likewise, other investigators who used different measurements found a trend but no clear positive shifts in stage of change among patients cared for trained physicians (14, 19). The questions used to categorize stages of change in smokers may not be sensitive enough to show progression through the stages in the trials conducted and settings used to date.

Our study has several strengths. The statistical approach was conservative; we used an intention-to-treat analysis, and the cluster analysis ensured that the effect of training was not related to specific residents. We trained the control residents in the smoking cessation intervention after the enrollment period, while study residents were in the follow-up period. Training control residents might have increased the frequency with which smoking interventions were administered to their patients and improved the quality of those interventions. This effect might create bias toward the null hypothesis and eventually underestimate the effectiveness of training. The research staff that collected data were blinded to the group allocation of residents and their patient assignments. Blinding of patients to the received intervention was crucial because self-reported counseling and smoking behavior are subjective outcomes (38). Finally, the proportion of smokers (32%) in the study sample is similar to that in the Swiss population (39), which suggests that our sample is fairly representative of patients attending Swiss primary care physicians.

Our study also has limitations. We validated abstinence at only one center because biochemical measures are expensive and difficult to implement in low-intensity interventions. However, biochemical validation may be unnecessary for trials of brief interventions with self-reports obtained by impersonal interviews (33, 40). Rates of false reports of abstinence are low because the pressure to give desirable answers is minimal (33). Furthermore, the low level of tobacco control in Switzerland (41) minimizes the social desirability bias. The reassuring results of sensitivity analysis, the conservative intention-to-treat approach, and the improvement of residents' practice in the intervention group make it unlikely that incomplete biochemical validation of abstinence influenced the effects of training. A Hawthorne effect may have occurred (42), but we minimized its likelihood by blinding residents and patients to the goal of the study. The response rate to the 1-year follow-up questionnaire (71%) was similar to that found in other studies (14, 16, 23, 43, 44). Long-term retention of skills in residents could not be assessed because within the 12 months after the intervention, most residents had left our institutions to open a private practice or to continue postgraduate training elsewhere. Other clinic staff (such as nurses, allied health professionals, and administrators) are unlikely to influence our results because they were neither taught nor involved in smoking cessation activities and health care delivery in both clinics relies essentially on physicians. Finally, organizational strategies, such as chart reminders, should reinforce the effect of training because they increase rates of performance of interventions by physicians and cessation of smoking among patients (10, 45).

Our results have important implications for medical education, clinical care, and public health. The U.S. Clinical Practice Guidelines (2) call for making research on effective elements of successful training programs a high priority. Our study shows that interactive learning methods, such as role-playing and practice with standardized patients, are effective and confirms that residency is a good time to train physicians in preventive care so that they can apply this knowledge later in their career (46–49). Finally, our results show that a positive effect on clinical outcome is mediated by improvement in processes of care (50).

We conclude that a physician training program in smoking cessation based on active learning of counseling skills with standardized patients is effective.

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J-Shaped Relationship between Blood Pressure and Mortality in Hypertensive Patients: New Insights from a Meta-Analysis of Individual-Patient Data

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Background: Population-based longitudinal studies of hypertension have usually shown a continuous and positive relationship between blood pressure and mortality. However, several studies in hypertensive patients receiving treatment have described this relationship as J-shaped, with an increased risk for events in patients with low blood pressure.

Objective: To assess the evidence for a J-shaped relationship between blood pressure and mortality and its relation to treatment.

Design: Meta-analysis of individual-patient data.

Setting: Seven randomized clinical trials from the INDANA (INdividual Data ANalysis of Antihypertensive intervention) database.

Patients: 40 233 persons with hypertension (mean follow-up, 3.9 years).

Intervention: Primarily β-blockers or thiazide diuretics versus placebo or no treatment.

Measurements: Diastolic and systolic blood pressure and number of cardiovascular, noncardiovascular, and all-cause deaths in yearly periods of follow-up.

Results: The analysis included data on 1655 deaths (56% cardiovascular). A J-shaped relationship between diastolic blood pressure and risk for death was observed for total and cardiovascular mortality in treated patients (nadir, 84 and 80 mm Hg, respectively) and untreated patients (nadir, 90 and 85 mm Hg, respectively). For noncardiovascular deaths, the relationship was J-shaped in the treated group (nadir, 84 mm Hg) and negative in the control group. Similar results were observed for systolic blood pressure. The presence of patients with wide pulse pressure did not explain these findings.

Conclusions: The increased risk for events observed in patients with low blood pressure was not related to antihypertensive treatment and was not specific to blood pressure–related events. Poor health conditions leading to low blood pressure and an increased risk for death probably explain the J-shaped curve.

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The benefit of antihypertensive treatments in reducing the risk for cardiovascular events in persons with high blood pressure has been well established (1–3). Despite this evidence, epidemiologic studies have shown that after adjustment for other risk factors, treated hypertensive patients with normalized blood pressure are still at higher risk for cardiovascular diseases than normotensive persons (4). Moreover, in clinical trials the observed risk reduction for coronary events has been smaller than could be expected from the log-linear relationship between blood pressure and risk according to epidemiologic data (5). Clinical trials have reported a 5- to 6-mm Hg difference between the diastolic blood pressures of treatment and control groups; the risk reduction of 14% (95% CI, 4% to 22%) for coronary events contrasts with the 20% to 25% reduction noted in epidemiologic reports. These discrepancies may be related to the existence of a J-shaped relationship between blood pressure and risk, in which treated patients with low blood pressure are at increased risk for coronary events.

The reports of a J-shaped relationship have come from longitudinal cohort studies of treated hypertensive patients (6–10) or clinical trial data on antihypertensive treatment groups and, in some trials, control groups (11–13). Interpretation of such results has varied. Some researchers have believed that overtreatment with blood pressure–reducing drugs may compromise coronary blood flow, especially in hypertensive patients with a history of myocardial infarction (14), while others have considered that the increased risk in patients with low blood pressure is independent of treatment and may be attributed to confounding factors related to deteriorating heath (12, 15, 16) or pulse pressure (17).

The INDANA (INdividual Data ANalysis of Antihypertensive intervention trials) project is a meta-analysis of individual-patient data collected from randomized clinical trials of antihypertensive medication versus pla-

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cebo or no intervention, with follow-up for cardiovascular events and deaths (18). INDANA offers the opportunity to further explore the J-shaped curve. Specifically, this database allows assessment of the evolution of risk according to achieved blood pressure separately for treated and untreated patients who in all other aspects are similar because of the randomization process.

Context

Lowering blood pressure in hypertensive patients decreases the risk for cardiovascular events. However, clinical trials show a discrepancy between observed and expected risk reduction, possibly because of a J-shaped relationship between blood pressure and risk reduction.

Contribution

The authors analyzed individual-patient data from seven randomized clinical trials of both treated and untreated hypertensive patients. All-cause death rates were higher among patients with high diastolic pressure and those with low diastolic pressure. Low diastolic pressure was associated with an increased death rate, even among untreated patients.

Implications

Excessive antihypertensive treatment may increase the death rate. Poor health may also cause low blood pressure and increase the risk for death.

–The Editors

METHODS

Study Sample

Data from five randomized clinical trials in elderly patients (Coope and Warrender [13]; European Working Party on High Blood Pressure in Elderly patients [EWPHE] [19], Medical Research Council trial in older adults [MRC2] [20], Systolic Hypertension in the Elderly Program [SHEP] [21], and Swedish Trial in Old Patients [STOP] [22]) and two trials in middle-aged patients (Hypertension Detection and Follow-up Program [HDFP] [23] and Medical Research Council trial in mild hypertension [MRC1] [24]) were pooled in a common file with information on baseline patient characteristics, blood pressure measurements over time, and occurrence of major clinical events.

For this analysis, we did not use the data from three other trials available at the INDANA coordinating center. First, the Multiple Risk Factor Intervention Trial (MRFIT) (25) could not directly relate a change in cardiovascular risk to a change in blood pressure because this study assessed the effects of cholesterol and smoking reduction in addition to that of blood pressure reduction. Next, we excluded the Australian National Blood Pressure Study (ANBPS) data (26) because of the risk for informative censoring (the end point was a combined criteria that included several soft events directly related to hypertension). Finally, the Veterans Administration–National Heart, Lung, and Blood Institute feasibility trial (VA–NHLBI) (27) had not been pooled in the database at the time of analysis but would have contributed only marginally to the overall results because few events were observed.

Blood Pressure Data

We did not include blood pressure at study entry in the analysis because these values were heavily conditioned by the trial-specific selection criteria for blood pressure. At least one blood pressure measurement per each year of follow-up was available. For trials that obtained several measurements per year, we used in our analysis the measurement obtained closest to the annual visit. Because systolic blood pressure in HDFP was measured only after 5 years of follow-up, this trial was not included in statistical analyses involving systolic blood pressure or pulse pressure.

Clinical Events and Follow-up

After study entry (baseline), the trials in the database monitored patients for occurrence of myocardial infarction, stroke, and death during a mean follow-up period ranging from 2.2 years in STOP to 5.8 years in MRC2. To make our results more robust, we focus on fatal events (classified as cardiovascular or noncardiovascular death). We did not analyze nonfatal events because they were monitored and reported less consistently than fatal events (for example, HDFP did not note the time to occurrence of strokes and EWPHE did not record nonfatal events after the occurrence of a nonfatal end point). In the analysis, follow-up for mortality started 1 year after randomization. For each subsequent yearly period, the risk for death was assessed according to the systolic and diastolic blood pressures obtained closest to the beginning of the year.

Table 1. **Patient Events in Each Study Recorded during Follow-up between 1 Year after Study Inclusion and End of Study Follow-up***

Study (Reference)	Patients	Mean Follow-up	Mean Age	Male Patients	Total Deaths	Cardiovascular Deaths
	n	*y*		%	*n*	
Coope and Warrender (13)	859	3.6	69.0	30.1	103	69
EWPHE (19)	732	4.2	71.5	29.5	128	71
HDFP (23)	10 819	3.9	50.7	53.9	375	215
MRC1 (24)	17 307	4.0	52.1	52.1	338	195
MRC2 (20)	4334	4.8	70.3	41.4	387	218
SHEP (21)	4678	3.4	71.6	43.1	275	131
STOP (22)	1504	1.3	75.6	36.7	49	27
All studies	40 233	3.9	57.5	48.9	1655	926

* EWPHE = European Working Party on High Blood Pressure in Elderly patients; HDFP = Hypertension Detection and Follow-up Program; MRC1 = Medical Research Council trial in mild hypertension; MRC2 = Medical Research Council trial in older adults; SHEP = Systolic Hypertension in the Elderly Program; STOP = Swedish Trial in Old Patients.

Statistical Analysis

As a first descriptive approach, we estimated the adjusted death rates by treatment group in successive categories of ongoing diastolic blood pressure (≤65, 66 to 75, 76 to 85, 86 to 95, 96 to 105, ≥106 mm Hg) and systolic blood pressure (≤120, 121 to 130, 131 to 140, 141 to 150, 151 to 160, 161 to 170, 171 to 180, ≥181 mm Hg) while controlling for any confounding effect of age, sex, study, and year of blood pressure measurement since study entry (28). For all patients, each successive 1-year period of follow-up was used to relate the blood pressure level at the beginning of that period to the risk for death during that period. This method allowed us to consider the influence of blood pressure on risk as it evolved over time. We used a Poisson linear regression model to relate the risk for dying (on a log scale) to the set of covariates (29). In addition to blood pressure, age, and time since entry (with each updated at every period), the other covariates were sex, history of medical events (myocardial infarction, stroke, and diabetes) before study entry, and smoking habits. Occurrence of nonfatal myocardial infarctions during follow-up was a further time-dependent covariate. To determine whether the relationship between blood pressure and risk was J-shaped, we fitted a model with both a linear and a quadratic (squared) term for blood pressure. This model assumes a curved relationship, with the risk for death decreasing to a minimum value with decreasing blood pressure before eventually increasing. Next, we estimated the minimum (nadir) and associated confidence interval from the coefficients of the linear and quadratic terms and their variance (30). Finally, to verify that an increase in risk with lower blood pressure was not a result of constraints of the quadratic model, we fitted blood pressure measurements at the left and right of the nadir with two independent curvilinear relationships, as proposed by Goetghebeur and Pocock (31). We repeated such modeling by using increasing nadir values (at intervals of 2 mm Hg for diastolic blood pressure and 5 mm Hg for systolic blood pressure) and determined the optimum nadir by the model with the best goodness of fit.

We performed all statistical analyses by using the SAS software package for Windows, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

The funding source had no role in the collection, analysis, and interpretation of the data or in the decision to submit the paper for publication.

RESULTS

Of the 40 777 patients randomly assigned to active treatment or control groups in the seven trials, we analyzed data on the 40 233 total patients alive at 1 year after study entry (Table 1). The mean follow-up was 3.9 years. Among the patients in our analysis, 48.9% (*n* = 19 692) were men and 27.7% (*n* = 11 107) were current smokers; 1312 patients (3.3%) had a history of myocardial infarction, 464 (1.1%) had a history of stroke, and 1420 (3.5%) had a history of diabetes mellitus. We could not include data on 31 995 1-year periods of follow-up (18.7%) in assessing a possible relation between fatal events and diastolic blood pressure because of missing blood pressure measurements. Overall, our analysis comprised data on 1655 deaths (56% of which were caused by cardiovascular events) during 126 908 total patient-years of follow-up.

One year after study entry, mean diastolic blood pressure in each trial was significantly lower in the active treatment group than in the control group; the mean 1-year difference in diastolic blood pressure between treatment groups ranged from 4.3 mm Hg in SHEP to 9.3 mm Hg in STOP (**Table 2**). During the subsequent years of follow-up, the diastolic blood pressure decreased slightly (mean, 0.5 mm Hg/y), but the difference between the active treatment and control groups remained.

As a first descriptive analysis, we plotted successive categories of diastolic and systolic blood pressure (**Figures 1 and 2**) for the total death rates in all seven trials combined, with adjustment for age, sex, and time (in years) since study inclusion. In the active treatment and control groups, both ends of the diastolic blood pressure distribution had higher rates of all-cause mortality. Among control patients, the overall death rate was lowest in patients whose achieved diastolic blood pressure was 86 to 95 mm Hg; in patients receiving active treatment, the lowest rate occurred in the 76- to 85-mm Hg category. Similar trends were observed separately for cardiovascular and noncardiovascular deaths. Especially noteworthy is the sharp increase observed in the noncardiovascular deaths at low levels of diastolic blood pressure in untreated patients (**Figure 1**). As shown in **Figure 2**, we found similar results for systolic blood pressure.

When we fitted a continuous quadratic model to the data, we observed strong evidence of a curvilinear relationship or a negative linear relationship between diastolic blood pressure and risk for all outcomes in active treatment and control patients (**Table 3**). We estimated the diastolic blood pressure corresponding to the lowest risk for death; we found this value to be lower for cardiovascular deaths compared with noncardiovascular deaths and consistently lower in the active treatment group compared with the control group.

By modeling the data to the left and right of the nadir with two independent quadratic functions, we found that the risk for total, cardiovascular, and noncardiovascular deaths in active treatment and control patients increased as diastolic blood pressure decreased. A curvilinear relationship was also shown between systolic

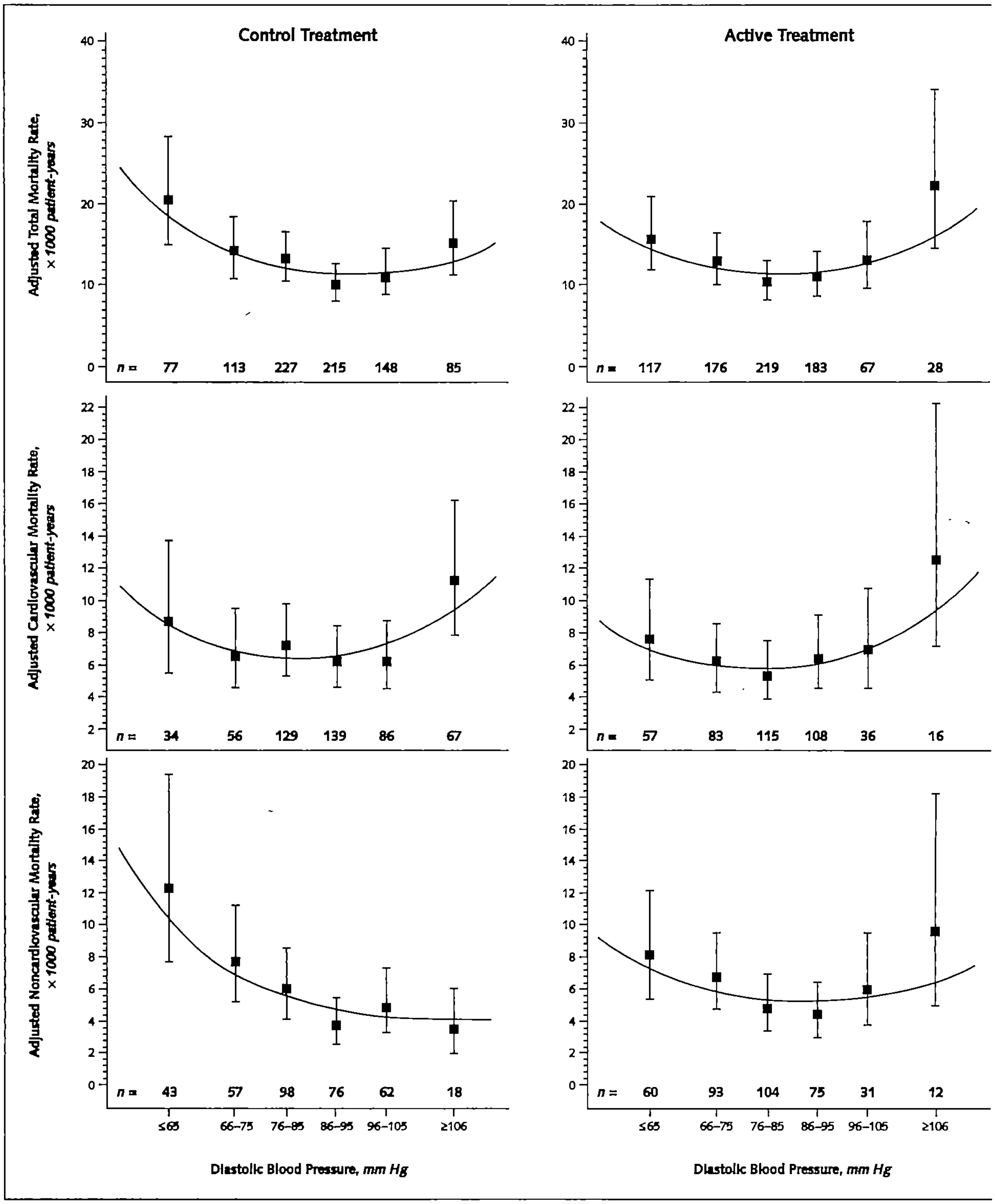
Table 2. **Blood Pressure 1 Year after Study Inclusion in Active Treatment and Control Groups***

Study (Reference)	Patients	Diastolic Blood Pressure	Systolic Blood Pressure	Mean Blood Pressure†
	n	← *mm Hg* →		
Coope and Warrender (13)				
Control group	439	94.2 ± 13.8	188.0 ± 23.7	125.5 ± 14.6
Active treatment group	406	87.1 ± 10.8	173.1 ± 20.6	115.7 ± 11.9
EWPHE (19)				
Control group	348	96.3 ± 12.2	173.3 ± 23.9	122.0 ± 14.5
Active treatment group	348	87.7 ± 9.8	152.5 ± 18.5	109.3 ± 10.8
HDFP (23)				
Control group	4883	94.0 ± 12.6	NA	NA
Active treatment group	5047	87.6 ± 11.0	NA	NA
MRC1 (24)				
Control group	8273	91.9 ± 9.2	148.4 ± 17.6	110.7 ± 10.7
Active treatment group	8244	86.9 ± 8.6	137.8 ± 16.5	103.9 ± 10.0
MRC2 (20)				
Control group	2098	86.5 ± 11.8	169.9 ± 17.2	114.3 ± 11.6
Active treatment group	2041	79.2 ± 11.0	153.9 ± 17.7	104.1 ± 11.1
SHEP (21)				
Control group	2053	74.0 ± 10.4	156.5 ± 17.2	101.5 ± 10.5
Active treatment group	2152	69.7 ± 9.3	142.6 ± 15.7	94.0 ± 9.2
STOP (22)				
Control group	719	97.1 ± 9.0	188.8 ± 19.0	127.6 ± 10.0
Active treatment group	732	87.8 ± 8.5	167.6 ± 19.4	114.4 ± 10.1

* Values with the plus/minus sign are the mean ± SD. EWPHE = European Working Party on High Blood Pressure in Elderly patients; HDFP = Hypertension Detection and Follow-up Program; MRC1 = Medical Research Council trial in mild hypertension; MRC2 = Medical Research Council trial in older adults; NA = not available at 1 year; SHEP = Systolic Hypertension in the Elderly Program; STOP = Swedish Trial in Old Patients.

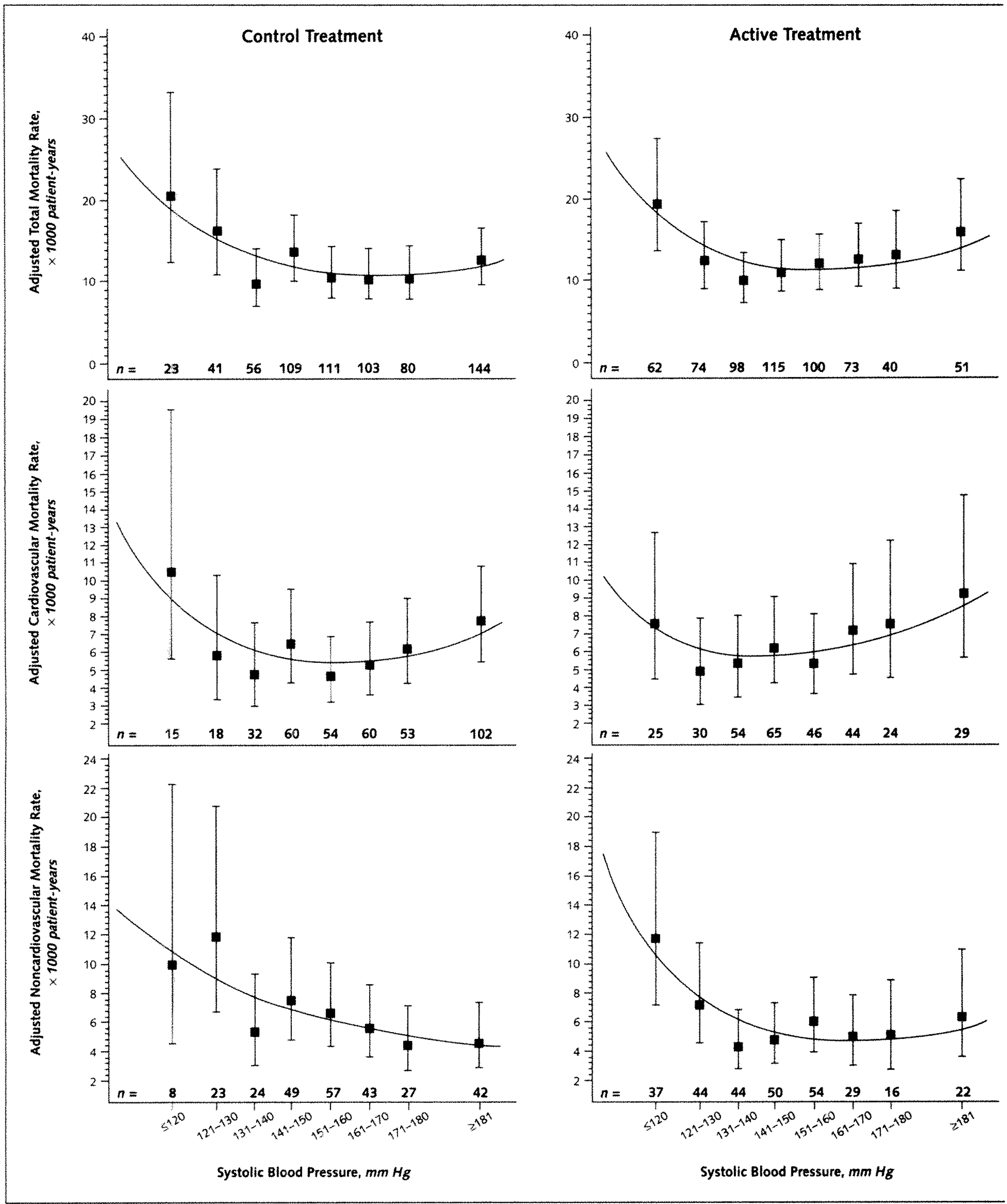
† Calculated as ([2 × diastolic blood pressure] + systolic blood pressure)/3.

Figure 1. **Age- and sex-adjusted rates of events in six categories of achieved diastolic blood pressure and predicted continuous relationship in active treatment and control groups.**



Event rates (*squares*) and 95% CIs (*bars*) are shown for the following categories of achieved diastolic blood pressure: ≤65, 66–75, 76–85, 86–95, 96–105, and ≥106 mm Hg. The number of events is shown below each bar.

Figure 2. **Age- and sex-adjusted rates of events in eight categories of achieved systolic blood pressure and predicted continuous relationship in active treatment and control groups.**



Event rates (*squares*) and 95% CIs (*bars*) are shown for the following categories of achieved systolic blood pressure: ≤120, 121–130, 131–140, 141–150, 151–160, 161–170, 171–180, ≥181 mm Hg. The number of events is shown below each bar.

blood pressure and total mortality (for active treatment and control patients), cardiovascular mortality (for control patients only), and noncardiovascular mortality (for active treatment patients). For noncardiovascular mortality, untreated patients showed a strong negative relationship. The double-quadratic model generally confirmed these results. As with diastolic blood pressure, the systolic blood pressures corresponding to the minimum risk were always lower in treated patients than in control patients.

When we repeated the analysis after censoring the follow-up periods subsequent to the occurrence of a nonfatal myocardial infarction, the results remained virtually unchanged. We calculated the following nadirs for the active treatment group: for total mortality, 83 mm Hg (CI, 74 to 91 mm Hg); for cardiovascular mortality, 78 mm Hg (CI, 63 to 87 mm Hg); and for noncardiovascular mortality, 90 mm Hg (CI, 77 to 125 mm Hg). In the control group, the nadir for total mortality was 93 mm Hg (CI, 87 to 102 mm Hg), and the nadir for cardiovascular mortality was 82 mm Hg (67 to 90 mm Hg); for noncardiovascular mortality, the relationship was strongly negative, as observed on all the data.

To assess whether results were sensitive to the level of the baseline diastolic blood pressure, we performed two subgroup analyses for total mortality: 1) in patients whose diastolic blood pressure at study entry was less than 90 mm Hg (median, 80 mm Hg) and 2) in patients with baseline diastolic blood pressure of 90 mm Hg or higher (median, 99). As shown in **Table 4**, the treated and control patients in these two groups had higher death rates at lower achieved diastolic blood pressures. The upturn to the left, as fitted by a curvilinear model, on the blood pressure data at the left side of the minimum point was in all cases statistically significant.

To control for the fact that higher pulse pressure levels in the lower categories of diastolic blood pressure may in itself explain the J-shaped curve, we fitted the model with pulse pressure as an additional covariable (using seven categories that ranged from <40 mm Hg to ≥90 mm Hg). In both the active treatment and control groups, the association between higher risk and decreasing diastolic blood pressure remained statistically significant ($P = 0.005$ and $P = 0.001$, respectively).

To verify whether patient characteristics could influence the results, we alternately stratified our data according to age at study entry (<70 years or ≥70 years), ongoing pulse pressure (<70 mm Hg or ≥70 mm Hg), and systolic blood pressure (<160 mm Hg or ≥160 mm Hg) and fitted the double quadratic model on total mortality. We found statistical evidence of an increased risk for death with lower achieved diastolic blood pressure in all strata, except in control patients with high systolic blood pressure (≥160 mm Hg), in treated patients with high pulse pressure (≥70 mm Hg), and in treated patients age 70 years or older.

The number of patients with a history of myocardial infarction or diabetes mellitus at baseline was insufficient to provide interpretable results in these two subgroups; exclusion of these patients did not modify the overall results.

DISCUSSION

A plethora of reports have described the shape of the relationship between blood pressure and risk. Some re-

Table 3. **Nadir Estimates and Statistical Evidence of a Quadratic Relationship between Last-Obtained Blood Pressure and Risk for Death***

Blood Pressure	Total Mortality		Cardiovascular Mortality		Noncardiovascular Mortality	
	Nadir Blood Pressure (95% CI)	*P* Value	Nadir Blood Pressure (95% CI)	*P* Value	Nadir Blood Pressure (95% CI)	*P* Value
	mm Hg		*mm Hg*		*mm Hg*	
Diastolic blood pressure						
Control group	94 (87–102)	0.001	84 (72–91)	0.001	–†	
Active treatment group	84 (76–91)	0.001	80 (67–89)	0.001	89 (77–114)	0.014
Systolic blood pressure						
Control group	169 (157–181)	0.001	156 (132–168)	0.001	–†	
Active treatment group	156 (145–166)	0.001	–†		164 (154–177)	0.001

* Adjusted for age, sex, smoking status; history of diabetes, stroke, and myocardial infarction; and coronary events during follow-up.
† Data not shown because the values provide no evidence of a J-shaped relationship.

Table 4. **Risk for Total Mortality in Six Categories of Achieved Diastolic Blood Pressure, according to Diastolic Blood Pressure at Study Entry and Treatment Group**

Baseline Diastolic Blood Pressure	Risk for Total Mortality (95% CI), according to Achieved Diastolic Blood Pressure					
	≤65 mm Hg	66–75 mm Hg	76–85 mm Hg	86–95 mm Hg	96–105 mm Hg	>105 mm Hg
	←——— *×1000 patient-years* ———→					
<90 mm Hg						
Control group	15.8 (9.8–25.2)	11.0 (7.1–17.0)	10.9 (7.2–16.4)	10.2 (6.4–16.3)	12.8 (6.5–25.2)	25.8 (9.7–68.6)
Active treatment group	8.7 (5.3–14.0)	6.4 (4.0–10.2)	4.8 (2.8–8.0)	8.2 (4.4–15.2)	23.6 (10.3–54.2)	–*
≥90 mm Hg						
Control group	30.3 (18.3–50.4)	15.9 (11.0–23.2)	13.7 (10.2–18.4)	9.8 (7.3–13.1)	11.2 (8.2–15.1)	14.9 (10.6–20.9)
Active treatment group	21.1 (13.4–33.1)	17.3 (12.7–23.6)	12.9 (9.7–17.2)	12.9 (9.5–17.4)	14.6 (10.2–21.0)	27.8 (17.7–43.7)

* The available data were insufficient for analysis.

ports have shown this relationship to be continuous and positive, while others have demonstrated an increased risk in participants with low blood pressure. Because many such investigations studied cohorts drawn from the general population, they could not investigate whether drugs that reduce blood pressure have harmed hypertensive patients when blood pressure is reduced below a certain level. Some studies focused specifically on cohorts of treated hypertensive patients who were followed for several years. However, these studies lacked control patients; thus, comparison with similar but untreated patients was impossible. Hence, several authors have criticized the conclusions drawn from the results of these studies, arguing that there may have been uncontrolled confounding factors, such as comorbid conditions, that exposed the patients with low blood pressure to a high risk for events (16, 32).

The INDANA database offered the opportunity to assess the shape of the relationship between risk for events and level of blood pressure in both treated and initially untreated hypertensive patients, with a power greater than those of the few clinical trials that have reanalyzed their data to explore this issue (12, 13). We believe that this database provides the best set of existing data from which new insights in the discussion on the J-shaped curve can be generated.

In the population of hypertensive patients included in our meta-analysis, the risk for fatal events was increased at lower blood pressures; we noted this observation in treated and untreated patients and for both cardiovascular and noncardiovascular deaths. Hence, our data support the conclusion that the J-shaped curve is at least partly independent of treatment and may be explained by patients with poor health conditions in the lowest categories of blood pressure. As a result of randomization, such patients were found in both treatment groups and therefore partly contribute to the J-shaped relationship observed in the active treatment group. The EWPHE trial investigators found similar results, in which patients with low blood pressure had decreased values for body mass index and hemoglobin—two indicators of poor health (12). Unfortunately, the INDANA database did not contain measurements of such markers over time. Results remained unchanged when we excluded patients with nonfatal coronary heart disease during follow-up or those with a history of myocardial infarction.

Baseline blood pressure is obviously an important consideration in determining whether the observed increase in mortality at decreasing blood pressures is primarily the result of the magnitude of change in pressure or the actual achieved blood pressure. However, an analysis involving baseline blood pressures of patients selected above or below some threshold (depending on the trial entry criteria) would introduce statistical problems (for example, because of misclassification or regression to the mean) (33) that are likely to bias the estimates of the relationship with risk. Despite these limitations, we analyzed patient data according to baseline diastolic blood pressure of less than or at least 90 mm Hg, and our findings illustrated a J-shaped curve for both these subgroups within the active treatment and control groups. Therefore, the magnitude of decrease in diastolic blood pressure from baseline did not influence the overall finding that the risk for death was increased in patients with a lower achieved diastolic blood pressure.

Increased death rates in untreated patients with low diastolic blood pressure could also be explained by the fact that most of these patients had isolated systolic hypertension (provided mainly by the SHEP and the MRC2 studies) and, hence, wide pulse pressure, which is associated with bad prognosis (17, 34, 35). However, after adjustment for pulse pressure, the death rates in patients with low achieved diastolic blood pressure increased, even for fixed levels of pulse pressure. The results of this analysis are similar to those of Somes (36), who entered diastolic blood pressure and systolic blood pressure jointly in the model. Somes found an increased risk for death with decreasing diastolic blood pressure in the active treatment group only. However, we have observed this relationship among the control patients as well. Age may be another important confounding factor, as the SHEP and the MRC2 studies contributed older patients in the lower categories of diastolic blood pressure. We believe that our adjustment for age in the model should have adequately controlled for this potential bias. In addition, we found evidence in subgroup analyses of a J-shaped curve (for total mortality) among patients with a pulse pressure less than 70 mm Hg and in patients younger than 70 years of age.

We determined the blood pressure at which the risk was lowest; we found that this value was lower in treated patients than in untreated patients. Let us assume that the J-shaped relationship observed in the untreated patients results from the following two factors: 1) a monotonic continuous positive relationship between blood pressure and risk, as reported by McMahon and colleagues (37) and 2) the presence of high-risk patients in the low blood pressure categories for reasons of reverse causality (ill heath causing low blood pressure). According to this hypothesis, patients receiving active treatment should be shifted downwards in terms of blood pressure and risk. Consequently, this should decrease the proportion of high-risk patients in the lower categories of blood pressure and hence shift the nadir in the treated group downward, as we observed. Below that point, the effect of high-risk patients with comorbid illness would predominate and invert the relationship with risk.

We used updated blood pressure measurements over time to relate blood pressure to the risk for events occurring during the following year. This modeling approach for analysis of the short-term effect of blood pressure was also used to examine data from the Framingham (15), HDFP (11), and Hypertension Optimal Treatment (HOT) (38) studies, and all these studies found some evidence of a J-shaped curve. However, the confounding effect of subclinical comorbid diseases in patients with low blood pressure is probably more pronounced over the short term than over the long term. Reanalyses of the cohort initially screened for the MRFIT study produced a J-shaped curve, in which events occurred during the first 2 years of follow-up, but a positive relationship was maintained thereafter (up to 16 years of follow-up) (39). Similarly, a J-shaped curve was observed only during the first 3 years of follow-up of a population-based cohort older than 65 years of age (16).

Our findings for systolic blood pressure were similar to those for diastolic blood pressure: We found no evidence of an increased risk for cardiovascular deaths with decreasing systolic blood pressure in treated patients. This observation may be related to the observation in a few studies (40, 41) that systolic blood pressure is more closely positively related than diastolic blood pressure to the risk for cardiovascular events, especially in elderly persons (42). Therefore, the relative effect of other confounding factors should be attenuated with systolic blood pressure. Moreover, because the HDFP data on ongoing systolic blood pressure were unavailable, we could not include this trial; consequently, the omission of the 98 cardiovascular deaths from the HDFP trial (of 415 overall in INDANA) decreased the power of our analysis.

Many researchers had expected the HOT trial to definitively determine the optimal blood pressure target for treating hypertensive patients. Unfortunately, direct comparison in that study of the three randomly allocated groups—with diastolic blood pressure targets of 80, 85, and 90 mm Hg—showed no significant difference in the risk for events, except for myocardial infarction, which showed a trend of decreased risk at lower blood pressure targets. Despite its inclusion of 18 790 patients, the HOT trial observed only 589 deaths—that is, 25% of the fatal events in our study. Hence, the secondary analysis of the HOT data (modeling the relationship between blood pressure and risk in patients receiving active treatment) was much less powerful than the current meta-analysis.

In conclusion, our findings indicate an increased risk for death among both treated and untreated hypertensive patients with low blood pressure, and this increased risk was apparent for cardiovascular deaths as well as for non–blood pressure–related events (noncardiovascular deaths). The blood pressure at which the risk for total mortality was lowest was 169/94 mm Hg in the control group and 156/84 mm Hg in the active treatment group. These results support the idea that the J-shaped curve is independent of treatment and is explained by other factors, such as poor health associated with low blood pressure.

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Mixed Hepatocellular–Cholestatic Liver Injury after Pioglitazone Therapy

Louis D. May, MD; Jay H. Lefkowitch, MD; Michael T. Kram, MD; and David E. Rubin, MD

Background: **Pioglitazone is an oral hypoglycemic agent in the thiazolidinedione class. Only one case of hepatotoxicity related to this agent has previously been reported.**

Objective: **To report the clinical course of a patient with hepatitis after therapy with pioglitazone.**

Design: **Case report.**

Setting: **A community hospital.**

Patient: **A 49-year-old diabetic man taking pioglitazone, 30 mg/d.**

Intervention: **Discontinuation of pioglitazone therapy.**

Measurements: **Serum aminotransferase and bilirubin levels, standard blood tests for causes of hepatitis and cirrhosis other than drug toxicity, and liver biopsy.**

Results: **After 6 months of pioglitazone therapy, significant hepatic dysfunction developed. Blood tests excluded viral, metabolic, and autoimmune disorders. Liver biopsy showed mixed hepatocellular–cholestatic injury compatible with drug toxicity. After treatment with pioglitazone was discontinued, liver enzyme values returned to normal.**

Conclusion: **Patients receiving pioglitazone may develop serious liver injury and should be observed for evidence of hepatitis.**

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See editorial comment on pp 480-483.

Thiazolidinedione hypoglycemic agents act primarily by decreasing insulin resistance and are useful in the management of type 2 diabetes mellitus (1). Troglitazone (Rezulin, Parke-Davis, Morris Plains, New Jersey) is a thiazolidinedione that has been associated with severe hepatic injury and has been withdrawn from the market in the United States and in Europe (2, 3). Rosiglitazone (Avandia, SmithKline Beecham [now GlaxoSmithKline], Philadelphia, Pennsylvania) is also in this class, and isolated cases of liver damage have occurred in patients during rosiglitazone treatment (4, 5). Pioglitazone (Actos, Takeda Pharmaceuticals North America, Lincolnshire, Illinois) is the newest thiazolidinedione drug; only one case of liver injury attributable to this agent has previously been published (6). We describe a patient who developed acute, reversible mixed hepatocellular–cholestatic liver injury while being treated with pioglitazone. This case has been reported to the manufacturer and to the U.S. Food and Drug Administration.

CASE REPORT

A 49-year-old electrician was referred for evaluation of hepatitis. He had a 6-year history of type 2 diabetes mellitus that was initially treated with glyburide, 5 mg twice daily. Subsequently, metformin, 850 mg three times daily, was added to his regimen. Six months before presentation, he began taking pioglitazone, 15 mg/d; 2 months before presentation, the daily dose was increased to 30 mg. Neither troglitazone nor rosiglitazone was administered. The patient's medical history included systemic arterial hypertension, which was well controlled by lisinopril (5 mg/d), and gastroesophageal reflux disease, for which the patient took a maintenance course of omeprazole (20 mg/d). The patient had been taking both drugs for 4 years. Liver chemistry profiles obtained at approximately 6-month intervals had been normal. Colonoscopy performed 3 years earlier for hemorrhoidal bleeding and diarrhea showed only diverticulosis. The patient had no history of gallstones or cholangitis.

Six weeks before our evaluation, the patient developed anorexia, nausea, and upper abdominal discomfort but had no rash or fever. He lost 2.7 kg (6 lb). Stool culture and examination for ova and parasites were negative. Results of liver enzyme tests and a complete blood count were normal. Peripheral blood smear showed a normal leukocyte differential count. One week before our evaluation, hyperglycemia was noted, and pioglitazone was increased to 45 mg/d.

Several days later, the patient noted scleral icterus and acholic stools. At that time, total bilirubin level was 97 μmol/L (5.7 mg/dL) (normal range, 5 to 17 μmol/L [0.3 to 1.0 mg/dL]), aspartate aminotransferase level was

Context

Thiazolidinedione agents are useful in the management of type 2 diabetes mellitus. Unfortunately, the first two drugs in this class, troglitazone and rosiglitazone, have been associated with hepatic injury. In 2001, clinicians reported a case of liver injury associated with pioglitazone, the newest thiazolidinedione.

Contribution

This report describes mixed hepatocellular–cholestatic liver injury in a patient who had been taking pioglitazone for 6 months. Liver enzyme values returned to normal 6 weeks after the patient discontinued pioglitazone therapy.

Implications

Hepatic injury can occur in association with pioglitazone as well as with the other drugs in this class. The frequency of this complication and its risk factors remain unknown.

—The Editors

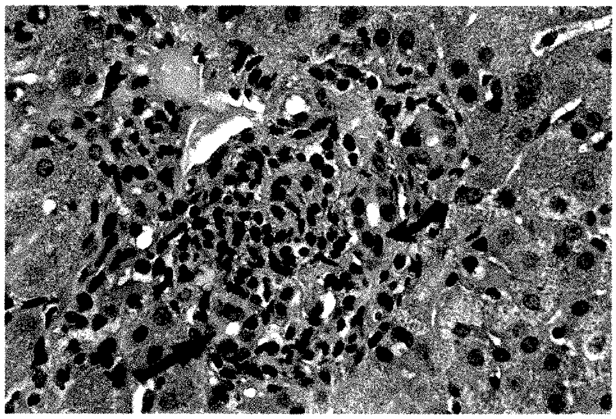
1.9 μkat/L (114 U/L) (normal range, 0 to 0.58 μkat/L [0 to 35 U/L]), alanine aminotransferase (ALT) level was 3633 nkat/L (218 U/L) (normal range, 0 to 583 nkat/L [0 to 35 U/L]), and alkaline phosphatase level was 5.2 μkat/L (normal range, 0.5 to 2.0 μkat/L). Pioglitazone therapy was discontinued. Results of abdominal sonography were normal, and results of serologic studies for hepatitis A, B, and C and for Epstein–Barr virus were negative. The patient was referred to us for hepatology consultation.

The patient reported no alcohol use; occupational exposure to hepatotoxins; or risk factors for hepatitis A, B, and C. He had no history of recreational drugs or travel. Physical examination revealed that he was icteric, but there were no cutaneous stigmata of liver disease. The abdomen was not tender, and he did not have hepatosplenomegaly or ascites; results of guaiac tests of the stool were negative. Liver chemistry findings had worsened. Total bilirubin level was 178 μmol/L (10.4 mg/dL), direct bilirubin level was 120 μmol/L (7.01 mg/dL), aspartate aminotransferase level was 7.8 μkat/L (467 U/L), ALT level was 8117 nkat/L (487 U/L), and alkaline phosphatase level was 11.2 μkat/L. Antinuclear, anti–smooth-muscle, and antimitochondrial antibodies were undetectable. Iron and iron saturation were normal, and there were no antibodies to cytomegalovirus. Results of repeated sonography and a computed tomography scan were normal. Hepatitis B surface antigen and antibodies to hepatitis A, B, and C and Epstein–Barr virus were again undetectable. Repeated complete blood count with differential was again normal.

Percutaneous liver biopsy was performed and showed mild centrilobular cholestasis in hepatocytes and bile canaliculi, accompanied by lymphocytic infiltrates in portal tracts. Portal infiltrates were diffuse but mild and consisted almost entirely of lymphocytes, with occasional neutrophils but no eosinophils. Interface hepatitis was absent. Several portal tracts contained damaged bile ducts, characterized by altered nuclear polarity and stratification and patchy intraepithelial lymphocytes (cholangiolitis) (**Figure 1**). The combination of cholestasis with portal inflammation and bile duct damage is a mixed hepatocellular–cholestatic type of liver injury that is compatible with drug hepatotoxicity (7).

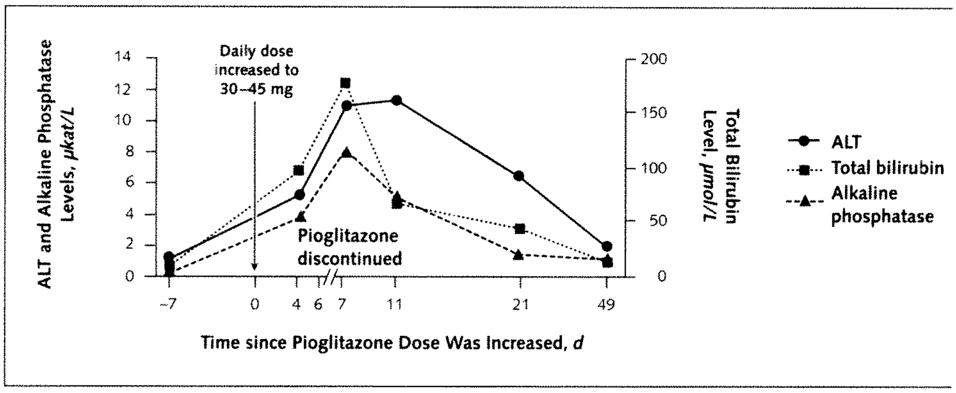
Because we suspected that pioglitazone was the hepatotoxic agent, the patient continued taking lisinopril, glyburide, metformin, and omeprazole throughout the illness. Liver chemistry findings improved gradually. Two weeks later, total bilirubin level was 45 μmol/L (2.66 mg/dL), aspartate aminotransferase level was 0.4 μkat/L (24 U/L), ALT level was 1417 nkat/L (85 U/L), and alkaline phosphatase level was 6.5 μkat/L. Results of liver tests continued to improve (**Figure 2**), and after

Figure 1. **Liver biopsy specimen showing mild portal lymphocytic inflammation.**



Several profiles of the bile duct are seen in this portal tract, showing mildly altered nuclear polarity (*curved arrow*) and intraepithelial lymphocytes (*straight arrow*). The lymphocyte is at 3 o'clock in the duct. (Hematoxylin–eosin; original magnification, ×325).

Figure 2. **Serum liver enzyme value associated with pioglitazone administration.**



ALT = alanine aminotransferase. To convert µkat/L to U/L, divide by 0.01667; to convert µkat/L to nkat/L, multiply by 1000; to convert µmol/L to mg/dL, divide by 17.104.

another 4-week interval, all liver chemistry findings were normal and the patient felt fine. Three months later, liver chemistry findings remained normal.

DISCUSSION

Pioglitazone is useful in the treatment of type 2 diabetes mellitus because it improves insulin sensitivity in muscle and adipose tissue and inhibits hepatic gluconeogenesis. It can be used as monotherapy or in combination with other oral hypoglycemic agents or with insulin. During premarketing drug trials, 0.26% of 1526 patients taking pioglitazone had asymptomatic increases in ALT level that were more than three times the upper limit of normal. Similar abnormalities were seen in 0.25% of 793 placebo-treated patients (8). The abnormalities were reversible and were not thought to be clearly related to therapy with pioglitazone. A single case report recently described a patient who developed hepatitis after 7 months of pioglitazone therapy; the patient had elevated serum ALT and alkaline phosphatase levels (6).

Several features of our case support pioglitazone as the cause of hepatic injury. First, other causes of acute hepatitis (including viral, autoimmune, and metabolic disorders), as well as biliary obstruction, were reasonably excluded. The data, including clinical presentation, previous colonoscopy results, normal results on ultrasonography, lack of history of inflammatory bowel disease, and resolution of liver test abnormalities after discontinuation of pioglitazone therapy, did not support a possible diagnosis of primary sclerosing cholangitis. Second, findings on liver biopsy were consistent with drug hepatotoxicity. Third, the patient began to steadily improve within a few days of stopping pioglitazone therapy and continued to improve until results of serum liver enzyme tests were completely normal. Because a repeated liver biopsy was not performed, we can only presume, not prove, that a morphologically normal liver was restored (9).

Hepatic injury due to troglitazone and rosiglitazone is believed to be idiosyncratic, and this is probably also the case with pioglitazone. However, the discrepancy between the many cases of troglitazone hepatotoxicity and the few cases attributable to rosiglitazone and pioglitazone could be related to specific features of troglitazone, such as its unique tocopherol side chain (10). Hepatotoxicity in our patient developed after 6 months of pioglitazone treatment; in the report by Maeda (6), hepatotoxicity was seen after 7 months. Although these time frames fall within the described range preceding troglitazone liver injury in men and women, they exceed the mean intervals of 88 and 63 days, respectively (2). The changes seen on liver biopsy in our patient were considerably milder than those reported in troglitazone toxicity, where severe centrilobular and bridging necrosis were common (2). Our patient had also received glyburide, metformin, lisinopril, and omeprazole but did not become ill until the addition of pioglitazone. Whether these agents together with pioglitazone can exert a combination effect or adversely alter pioglitazone metabolism was difficult to assess in this case. Although a therapeutic trial with corticosteroids was considered, the absence of both peripheral and hepatic eosinophilia and the rapid improvement after discontinuation of pioglitazone therapy made this unnecessary.

In summary, we describe the clinical course and findings on liver biopsy in a patient with significant hepatic injury associated with pioglitazone. Physicians should be aware that this frequently prescribed agent is potentially hepatotoxic. Patients receiving this drug should be monitored for evidence of liver dysfunction, particularly during the first year of therapy.

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Update in Women's Health

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In selecting the articles for this Update, we systematically reviewed the literature and consulted our colleagues to identify important papers on women's health published in 2000. We critically examined the content and methods of the studies identified and selected 10 articles that had potential to affect clinical practice and reflected a broad range of topics pertinent to women's health. These articles cover six areas: issues affecting women of reproductive age, breast cancer treatment, hormone replacement therapy, osteoporosis, cancer screening, and sexual dysfunction.

Issues Affecting Women of Reproductive Age

Important articles of significance for women of reproductive age included an examination of the significance of asymptomatic bacteriuria in young sexually active women, an analysis of factors involved in delayed access to HIV care, and an assessment of the association between oral contraceptive use and breast cancer risk in patients with a family history of breast cancer.

More Than 90% of Cases of Asymptomatic Bacteriuria Resolve without Developing into an Infection

Hooton TM, Scholes D, Stapleton AE, et al. A prospective study of asymptomatic bacteriuria in sexually active young women. N Engl J Med. 2000;343:992-7. [PMID: 11018165]

Although asymptomatic bacteriuria is common in young women, little is known about its pathogenesis, natural history, risk factors, and temporal association with symptomatic urinary tract infections (UTIs). To evaluate these factors, Hooton and colleagues conducted a prospective cohort study of nonpregnant women 18 to 40 years of age. The 796 participants were patients at a university student health center or a health maintenance organization (HMO) in Seattle, Washington, from 1989 to 1994 and were about to start or had just started a new method of contraception.

Baseline evaluation included a standardized interview, testing of a midstream urine specimen to evaluate pyuria and bacteriuria, and testing of blood and saliva samples to determine ABO-blood group secretor status. Women kept diaries to record the days on which the following occurred: sexual intercourse, use and type of contraception, vaginal and urinary symptoms, and antibiotic use. They also provided urine samples monthly for 6 months.

Asymptomatic bacteriuria was defined as the presence of at least 10^5 colony-forming units (CFUs) of a urinary pathogen per mL in a culture obtained from an asymptomatic woman. A symptomatic UTI was defined as 1) the presence of dysuria, urinary frequency, or urgency and 2) at least 10^2 CFUs of a urinary pathogen per mL, a health care provider diagnosis of UTI, or antibiotic treatment for urinary symptoms.

The prevalence of asymptomatic bacteriuria was 5% (95% CI, 4% to 6%) in the university group and 6% (CI, 5% to 8%) in the HMO group; 22% of patients had at least one episode of asymptomatic bacteriuria. Episodes of asymptomatic bacteriuria lasting longer than 2 months were rare, occurring in only 3 participants (0.8%) in the university group and 1 participant (0.2%) in the HMO group.

For both groups combined, 8% of the 295 cultures with 10^5 or more CFUs of urinary pathogens per mL were followed by a symptomatic UTI within 1 week, compared with 1% of cultures with fewer than 10^5 CFUs/mL ($P < 0.001$). Of the 34 cultures with bacteriuria and pyuria, a symptomatic UTI occurred in 15% within 1 week. In multivariate analyses, recent use of a diaphragm plus spermicide and recent sexual intercourse were strongly associated with asymptomatic bacteriuria in both groups. The *Escherichia coli* strains that caused asymptomatic bacteriuria did not differ from those that caused symptomatic UTIs.

The researchers concluded that asymptomatic bacteriuria is common in young sexually active women but that it rarely persists. More than 90% of cases resolved without developing into an infection. For the internist, the important message is that asymptomatic bacteriuria in young sexually active women is common and usually transient and thus does not have to be treated. Given the small percentage of cases of bacteriuria that develop into symptomatic UTIs, routine screening urinalyses are not warranted in healthy sexually active women. The reason that symptomatic UTIs occur in only a small proportion

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of women with bacteriuria is not clear. The development of a UTI may reflect additional virulence factors not measured in this study, or may result from a complex interplay between expression of virulence factors and variation in the host environment.

Women Are More Likely Than Men To Delay HIV Care

Stein MD, Crystal S, Cunningham WE, et al. Delays in seeking HIV care due to competing caregiver responsibilities. Am J Public Health. 2000;90:1138-40. [PMID: 10897195]

To assess the characteristics of HIV-positive persons who delay seeking medical care, Stein and colleagues studied 2864 patients, 18 years of age or older, who had sought non–emergency department HIV care between 1996 and 1997. Study participants, recruited from 196 providers in 79 metropolitan and rural areas, completed a one-time computer-assisted cross-sectional interview. Direct questions concerned age, race, education, insurance status, intravenous drug use, household composition, and other HIV-infected household members. The following question assessed delay in medical care due to caregiving responsibilities: "In the last 6 months, have you ever put off going to the doctor for HIV care because taking care of someone else was more important to you?" The investigators performed bivariate analyses and multiple logistic regression modeling to determine whether demographic, clinical, and household composition variables were associated with delay in seeking care.

Twenty-three percent of the 2864 participants were women. Women were more likely than men to be living with children younger than 17 years of age (45% vs. 6%; $P < 0.01$) and were more likely to report delay in HIV care as a result of caregiving in the previous 6 months (14% vs. 8%; $P < 0.001$). The first logistic regression model did not include CD4 cell count or report of the presence of a child in the household. This model found that being a woman (odds ratio, 1.7 [CI, 1.2 to 2.4]), having no medical insurance (odds ratio, 2.2 [CI, 1.3 to 3.5]), and having public insurance (odds ratio, 2.2 [CI, 1.3 to 3.7]) were associated with delay in seeking HIV care. Race, education, and intravenous drug use were not associated with delay in care. In the model that included CD4 cell count greater than 0.500×10^9cells/L and the presence of a child in the household, being a woman was no longer significant (odds ratio, 1.3 [CI, 0.8 to 1.8]), but having a child in the household was associated with delay in seeking care (odds ratio, 1.8 [CI, 1.2 to 2.6]). A CD4 cell count greater than 0.500×10^9cells/L was also associated with delay in care (odds ratio, 1.9 [CI, 1.3 to 2.8]).

The researchers concluded that delay in seeking care was associated with having public insurance or no insurance and with a CD4 cell count greater than 0.500×10^9cells/L and that women were more likely to delay care than men. Most of the difference in delay in care between women and men was attributable to the presence of children in the household and women delaying care for themselves because of caregiving responsibilities. Lack of insurance or reliance on public insurance, a marker for low-income status, was also associated with delay in seeking care. Women with HIV infection, especially those with public or no health insurance, need supportive services to seek health care for themselves. Health care providers should recognize the caregiving responsibilities of their patients, especially low-income women, and work to alleviate the effect of these responsibilities in their own care. When on-site child care is not available, telephone contact, extended hours, and home services may provide some avenues to ensure that a woman's health needs are not delayed.

Women Who Have Used High-Dose Contraceptives and Have a First-Degree Relative with Breast Cancer May Be at Higher Risk for the Disease

Grabrick DM, Hartmann LC, Cerhan JR, et al. Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. JAMA. 2000;284:1791-8. [PMID: 11025831]

In a retrospective follow-up of family members of a historical cohort study, Grabrick and colleagues examined whether family history influences breast cancer risk in women who use oral contraceptives. The original study looked at a population-based cohort with 504 incident cases of breast cancer between 1944 and 1952. The follow-up, conducted from 1991 to 1996, studied all first-degree (sisters and daughters) and second-degree (granddaughters and nieces) relatives and persons related by marriage (for example, a woman married to the son or brother of woman with breast cancer). Living participants able to respond self-reported their history of breast cancer and information on oral contraceptive use over the telephone.

The response rate for 92% of the families was 93%.

The investigators used Cox proportional hazards regression to analyze the data. Analyses controlled for year of birth, known breast cancer risk factors, duration of oral contraceptive use, and mammography use. The authors stratified the analysis by contraceptive use before and after 1975 because formulations used before 1975 more commonly contained high-dose estrogen (≥50 μg of ethinyl estradiol) whereas those used thereafter more often contained low-dose estrogen (≤35 μg of ethinyl estradiol). The authors also stratified analyses by number of family members with breast cancer; they defined high-risk families as those in which three or more family members had breast or ovarian cancer.

The authors found 239 cases of breast cancer. The overall association of breast cancer and ever use of oral contraceptives in the entire cohort was weak (relative risk, 1.4 [CI, 1.0 to 2.0]). First-degree relatives who had used oral contraceptives had a significantly increased risk for breast cancer than nonusers (relative risk, 3.3 [CI, 1.6 to 6.7]). No association between oral contraceptive use and breast cancer was seen in second-degree relatives (relative risk, 1.2 [CI, 0.8 to 2.0]) or persons related by marriage (relative risk, 1.2 [CI, 0.8 to 1.9]).

None of the following potential confounders changed the association: parity, age at birth of first child, education, body mass index, alcohol intake, smoking, age at menarche or menopause, oophorectomy, or number of mammograms. The risk for breast cancer from oral contraceptive use was 4.6 (CI, 2.0 to 10.7) in first-degree relatives who had at least three blood relatives with breast or ovarian cancer and 11.4 (CI, 2.3 to 56.4) in first-degree relatives who had at least five blood relatives with breast or ovarian cancer. The study had insufficient power to analyze risk based on estrogen dose in the oral contraceptive.

In summary, oral contraceptive use by women who have first-degree relatives with breast cancer was associated with a more than threefold risk for breast cancer. Women who had second-degree relatives with breast cancer did not have an increased risk. The findings were even more pronounced in families at high risk for ovarian and breast cancer.

The study's strengths are the use of a population-based breast cancer cohort, a high participation rate, validation of self-reports, and control for potential confounders. First-degree relatives, however, had taken oral contraceptives when the dose of ethinyl estradiol was higher (50 to 100 μg) than in today's preparations (<35 μg); therefore, findings in this group preclude a statement about the risk from current low-dose oral contraceptives. Clinicians should consider this association, however, when counseling women who have first-degree relatives with breast cancer about contraception options. For women from high-risk families, the potential increased risk for breast cancer associated with oral contraceptives must be balanced against the beneficial effect of oral contraceptives in decreasing the risk for ovarian cancer.

Breast Cancer Treatment

Women with Metastatic Breast Cancer Who Receive High-Dose Chemotherapy plus Stem-Cell Transplants Do Not Survive Longer Than Those Receiving Conventional Chemotherapy

Stadtmauer EA, O'Neill A, Goldstein LJ, et al. Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. Philadelphia Bone Marrow Transplant Group. N Engl J Med. 2000;342:1069-76. [PMID: 10760307]

Stadtmauer and colleagues' randomized trial evaluated the benefit of high-dose chemotherapy plus autologous bone marrow transplantation compared with conventional chemotherapy in women with metastatic breast cancer who had already achieved an induction response. The study sample consisted of women, 18 to 60 years of age, with non–central nervous system metastatic breast cancer who had not previously received chemotherapy for metastatic disease.

Participants who achieved an induction response were randomly assigned to the experimental group (high-dose chemotherapy with cyclophosphamide, carboplatin, and thiotepa, followed by autologous stem-cell transplantation) or the control group (conventional-dose therapy with cyclophosphamide, methotrexate, and fluorouracil) for up to 2 years.

The primary end point was survival. Secondary end points included time to progression and moderate to severe adverse side effects. The study had 85% power to detect doubling of median survival.

Of the 553 women initially enrolled for induction chemotherapy, 268 (48%) were ineligible for randomization, 208 did not achieve partial or complete remission, 57 did not meet other eligibility criteria, and 3 died. Of 285 patients with partial or complete responses, only 199 (70%) were randomly assigned; 48 withdrew consent, and 38 withdrew from the study for unknown reasons.

The overall 3-year survival rate was 32% in the chemotherapy plus transplant group compared with 38% in the conventional chemotherapy group; median time to progression was 9.6 months and 9.0 months, respectively ($P > 0.2$). The rate of moderate to severe adverse reactions, including leukopenia, thrombocytopenia, anemia, and infection, was higher in the chemotherapy plus transplant group.

The authors concluded that, contrary to the initial promise of uncontrolled trials (1–3) and one randomized trial later discredited for falsified data (4), bone marrow transplantation offers no benefit over conventional therapy for metastatic breast cancer. This study illustrates that (despite the desperation of critically ill patients), women are not well served when we bypass clinical trials and offer experimental therapy off-trial. Moreover, it confirms the wisdom of performing controlled clinical trials early in the lifetime of new treatments.

Hormone Replacement Therapy

Estrogen–Progestin Use May Be Associated with an Increased Risk for Breast Cancer Compared with Estrogen Use Alone

Schairer C, Lubin J, Troisi R, et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA. 2000;283:485-91. [PMID: 10659874]

The preponderance of epidemiologic data suggests that women who use hormone replacement therapy have an increased risk for breast cancer (5, 6). Whether the combination of estrogen plus progestin confers a greater risk than does estrogen alone is unknown. Schairer and colleagues conducted a cohort study using follow-up data (1980 to 1995) from the Breast Cancer Detection Demonstration Project, in which 46 355 postmenopausal women participated.

The authors considered the following confounders in the analysis: race, period of follow-up, age at first live birth, age at menopause, family history of breast cancer, history of benign breast disease, clinical breast examinations, mammographies, education, and body mass index. Outcomes were cases of breast cancer.

Compared with no use, ever use of estrogen and estrogen–progestin were both associated with slightly increased relative risk for breast cancer (relative risk, 1.1 [CI, 1.0 to 1.3] and 1.3 [CI, 1.0 to 1.6], respectively). Compared with nonusers, the relative risk for breast cancer increased by 0.01 (CI, 0.002 to 0.03) per year of use of estrogen alone and 0.08 (CI, 0.02 to 0.16) per year of use of estrogen–progestin.

Schairer and colleagues categorized women by body mass index: 24.4 kg/m^{2}or less and greater than 24.4 kg/m^2. Associations with duration of estrogen or estrogen–progestin use were seen only in women with a lower body mass index.

The authors conclude that estrogen–progestin use may be associated with an increase in breast cancer risk beyond the risk associated with estrogen alone. The increased risk for breast cancer associated with estrogen use only and estrogen–progestin use may be most significant in lean women.

Although the study results suggest an increased risk of estrogen–progestin compared with estrogen alone, the overlapping confidence intervals indicate that the results are also compatible with no difference in risk. In support of the authors' conclusions, however, Ross and colleagues' recent case–control study (including 1897 case-patients and 1637 neighborhood controls) showed similar results (6). In that study, the odds ratio was 1.24 (CI, 1.07 to 1.45) per 5 years of use of combined estrogen–progestin and 1.06 (CI, 0.97 to 1.15) for estrogen use only. Risk estimates were higher for women who took sequential estrogen–progestin therapy than for those who took continuous combined estrogen–progestin therapy, but the differences were not statistically significant (6).

Clinicians should consider the increased risk for breast cancer when talking with patients about risks and benefits of hormone replacement therapy. Given the extensive data on the risk for endometrial cancer with unopposed estrogen, clinicians should not advise women to discontinue progestin therapy and continue taking unopposed estrogen solely to avoid breast cancer. No conclusive evidence favors one progestin regimen over another.

Functional or Cognitive Outcomes Did Not Improve after Estrogen Treatment in Women with Established Alzheimer Disease

Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. JAMA. 2000;283:1007-15. [PMID: 10697060]

To determine whether estrogen replacement therapy affects global, cognitive, or functional decline in women with mild to moderate Alzheimer disease, Mulnard and colleagues conducted a randomized clinical trial at 32 U.S. sites.

The participants were 120 women older than 60 years of age with mild to moderate Alzheimer disease and a Mini-Mental State Examination (MMSE) score of 12 to 28. All participants had had a hysterectomy. The investigators randomly assigned women to receive 0.625 mg of estrogen, 1.25 mg of estrogen, or placebo. The main outcome was change in the Alzheimer Disease Cooperative Study's version of the Clinical Global Impression of Change 7-point scale; other outcomes included MMSE score, Clinical Dementia Rating Scale, mood measure, specific cognitive domains (memory, attention, and language), motor function, and activities of daily living. Throughout the trial, a caregiver administered the investigational agent.

Because findings in the two estrogen groups did not significantly differ, the investigators combined them into one group. The study had 81% power to detect a 29% difference in the proportion of patients whose cognitive function worsened in the two groups; the authors chose a large effect size to ensure clinical significance.

A total of 97 women completed the study. Twenty-five women withdrew: 7 in the placebo group (2 because of adverse events), 7 in the 0.625-mg estrogen group (7 because of adverse events), and 9 in the 1.25-mg estrogen group (4 because of adverse events). At 12-month follow-up, 74% of patients receiving placebo had worse scores on the Alzheimer Disease Cooperative Study's version of the Clinical Global Impression of Change compared with 80% of those in the combined estrogen group; this difference was not significant. The difference in the clinical dementia rating score significantly favored the placebo group (mean change, 0.5 for the combined estrogen group vs. 0.2 for placebo; $P < 0.01$). Most secondary cognitive outcome variables did not significantly differ between groups. Four cases of deep venous thrombosis and four episodes of vaginal bleeding developed in the estrogen group.

The results suggest that estrogen does not improve functional or cognitive outcomes in women with established Alzheimer disease. On the basis of these results, estrogen has no role in treating established Alzheimer disease. This study, however, provides no information on whether estrogen may be useful in the primary prevention of the disease. The role of estrogen for primary prevention is being assessed in the Women's Health Initiative and the Preventing Postmenopausal Memory Loss in Alzheimer's with Replacement Estrogens Study.

Osteoporosis

Osteoporosis remains an important topic in women's health. Previous Updates in Women's Health reviewed new pharmacologic therapies for postmenopausal women with osteoporosis. As the number of new therapies grows, questions on how to monitor the ongoing effectiveness of these therapies emerge. We review a study that provides important information on monitoring therapy by using bone mineral density. We also report on a new potential risk factor for falls and fractures in elderly women.

Treatment for Osteoporosis Should Continue for Patients Who Lose Bone Mineral Density during the First Year of Osteoporosis Therapy

Cummings SR, Palermo L, Browner W, et al. Monitoring osteoporosis therapy with bone densitometry: misleading changes and regression to the mean. Fracture Intervention Trial Research Group. JAMA. 2000;283:1318-21. [PMID: 10714731]

There has been debate about how often to repeat bone densitometry after initial screening and how the results should affect therapeutic decisions. Cummings and colleagues analyzed two randomized, placebo-controlled trials (the Fracture Intervention Trial [FIT] and the Multiple Outcomes of Raloxifene Evaluation [MORE] trial) to assess whether women who lose bone mineral density (BMD) during the first year of osteoporosis treatment continue to lose BMD if treatment continues for more than 1 year. The FIT participants—postmenopausal women with a femoral neck BMD of 0.68 g/cm^2 or less—were randomly assigned to receive 5 mg of alendronate per day or placebo for 2 years. Women in the MORE study were postmenopausal and 80 years of age or younger; their BMD of the femoral neck or lumbar spine was at least 2.5 SDs below the mean for normal young adult women, or they had one moderate or two mild vertebral fractures. They were randomly assigned to receive 60 or 120 mg of raloxifene per day or placebo for 3 years. In both studies, BMD was measured at baseline, 12 months, and 24 months.

In FIT, women receiving alendronate gained an average of 2.2% in total hip BMD and 4.5% in spine BMD. Most women in this group (82%) gained BMD in the first year, but in 1.4% of the participants total hip BMD decreased by more than 4%. In both the alendronate and placebo groups, those who lost the most BMD during the first year of alendronate treatment were most likely to gain BMD during the second year. Changes in spinal BMD did not predict changes in hip BMD. Results were similar for women who received raloxifene: Those who lost BMD in the first year were most likely to gain BMD in the second year, and those who gained the most BMD in the first year were most likely to lose BMD in the second year.

Thus, the few patients who lose BMD during the first year of alendronate or raloxifene treatment are likely to gain BMD with continued treatment. This phenomenon shows the principle of regression to the mean: Individuals with measurements that differ from the mean for a population tend to have repeated measurements that are closer to the mean, and this tendency is greatest for those whose initial measurements are farthest from the mean. The same phenomenon is true for women receiving placebo.

The results of this study have several practical implications. First, the findings suggest that treatment should be continued in patients who initially lose BMD, because most patients gain BMD with continued treatment. Loss of BMD, however, should still prompt questions about adherence to therapy and about whether patients are taking the medication correctly. Second, unusually large gains in BMD after the first year of treatment and loss of BMD the second year probably reflect the random-error measurement of BMD rather than resistance to the medication. Third, change in measurement at a second skeletal site does not appear to predict change in hip BMD during the second year of treatment. Fourth, in women who are not receiving therapy, unexpected losses or unusually large changes in BMD are also probably due to random measurement error. Clinicians should consider confirming large changes in BMD with repeated testing before changing management. Finally, this study calls into question the value of monitoring osteoporosis treatment with yearly measurement of BMD. As with any diagnostic test, if the results do not change management, it may be best not to order the test. Although measurement of BMD may be valuable in prompting questions about adherence and proper use of medication among patients with BMD loss, physicians can incorporate these questions into routine follow-up examinations.

Urge Incontinence Is a Major Risk Factor for Falls and Consequent Fractures

Brown JS, Vittinghoff E, Wyman JF, et al. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc. 2000;48:721-5. [PMID: 10894308]

Falls are associated with substantial morbidity and mortality in elderly persons; approximately 10% to 15% of falls cause fracture. Identifying elderly persons at risk for falling and intervening to reduce modifiable risks are likely to improve clinical outcomes. Brown and colleagues studied whether urinary incontinence is associated with falls and fractures in older women. Participants in the Study of Osteoporotic Fractures were community-dwelling white women, 65 years of age and older, recruited from 1986 through 1988 from four geographic areas of the United States.

A self-administered questionnaire given in 1994–1996 asked about type and frequency of incontinence in the preceding 12 months. Urge incontinence was defined by the following statement: "When I have the urge to urinate and can't get to the toilet fast enough." Stress incontinence was defined as "Leakage of urine when I cough, sneeze, laugh, lift, stand up or exercise."

The investigators mailed women postcards every 4 months and asked them to contact the study staff if any falls or fractures occurred. Telephone interviews assessed the circumstances of the fall or fracture. The authors confirmed all fractures by reviewing radiographs.

The authors created multivariate models using repeated-measures methods to predict falls and nonspine fractures as outcomes. Models were adjusted for age; frailty; living situation; medical history; medication use; falls in the previous year; alcohol and caffeine use; and regular walking exercise and functional assessments of balance, strength, and speed.

During follow-up, 25% of women reported weekly urge incontinence, 19% reported weekly stress incontinence, and 12% reported both types of incontinence. Fifty-five percent reported at least one fall, and 8.5% had at least one fracture. The annual fracture rate was 3%.

In the multivariate models, urge incontinence was associated with falls (odds ratio, 1.26 [CI, 1.14 to 1.40]) and fractures (odds ratio, 1.34 [CI, 1.06 to 1.69]), but stress incontinence was not. There was a dose–response effect: The risk for falls and fractures was greater with more frequent urge incontinence.

In conclusion, in this community-based group of women, urge incontinence, but not stress incontinence, was associated with increased risk for both falls and fractures. A dose response was seen—higher risks for falls and fractures were associated with more frequent urge incontinence. On the basis of a fall rate of 25%, the attributable risk for fractures due to urge incontinence was 0.9%; the attributable risk percentage was 30%. Because incontinence appears to be a major risk for falls—and therefore fractures—in community-dwelling elderly women, physicians should consider asking patients about symptoms of urge incontinence and initiating therapy not only to relieve symptoms but to possibly prevent fractures.

Cancer Screening

Cytologic Test Results in Previously Screened Postmenopausal Women Are More Likely To Be False Positive Than True Positive

Sawaya GF, Grady D, Kerlikowske K, et al. The positive predictive value of cervical smears in previously screened postmenopausal women: the Heart and Estrogen/progestin Replacement Study (HERS). Ann Intern Med. 2000;133:942-50. [PMID: 11119395]

Because the incidence of cervical dysplasia declines with age, the screening of postmenopausal women with previously normal Papanicolaou (Pap) smears is controversial. In addition, data on whether hormone replacement therapy affects cervical cytologic findings are conflicting. Sawaya and colleagues sought to determine the predictive value of an abnormal cervical smear in postmenopausal women with recent normal Pap smears and to determine the independent effect of oral estrogen plus progestin on the development of cytologic abnormalities.

Cervical smears were collected prospectively during the Heart and Estrogen/progestin Replacement Study (HERS), a randomized, double-blind trial of 2763 postmenopausal women younger than 80 years of age with coronary artery disease and an intact uterus. Women received estrogen plus progestin or placebo. Cervical smears were obtained during annual visits. Abnormal smears were defined as those showing atypical squamous cells of unknown significance (ASCUS), atypical glandular cells of undetermined significance (AGCUS), low-grade squamous intraepithelial lesion (LGSIL), or high-grade squamous intraepithelial lesion (HGSIL). The investigators obtained information on the 2-year follow-up of abnormal Pap smears by using a questionnaire sent to clinical personnel at each study site and data collected as part of the study protocol. Copies of diagnostic test results and pathology reports were also obtained.

The final histologic status for each woman was classified as normal (a nondysplastic process, such as atrophy, cervicitis, inflammation), low-grade histologic condition (human papillomavirus or grade I cervical intraepithelial neoplasia [CIN I]), high-grade histologic condition (CIN II to III or vaginal intraepithelial neoplasia grades II to III), and unknown (results could not be located or did not meet criteria for normal).

Of the 2561 women with normal baseline smears (mean age, 66.7 years), 89% were white and 60% had 12 or fewer years of education. Seventy-eight women (3%) had an abnormal smear 1 year after the baseline smear, and 32 (1.4%) had an abnormal smear 2 years after the baseline smear.

Most new cytologic abnormalities were ASCUS (67.3%) and AGCUS (21.0%). A total of 231 interventions were done, including 112 cervical smears, 33 colposcopies, and 21 cervical biopsies. Ninety-four (85.5%)

of the final histologic abnormalities were normal; 6 were a low-grade histologic condition, 2 were high-grade histologic conditions (CIN I or II and grade III vaginal intraepithelial neoplasia), 1 was endometrial hyperplasia without atypia, and 7 were unknown. No women had CIN II or III or invasive cancer.

The positive predictive value of any smear abnormality (ASCUS, AGCUS, LGSIL, HGSIL) predicting a final high-grade cervical histologic abnormality was 0.0% (CI, 0% to 5%) within the first year of a normal Pap smear and 0.9% (CI, 0.0% to 3.0%) (1 of 110 women) within 2 years of the normal Pap smear. In hormone-treated women, the incidence of new cytologic abnormalities was nonsignificantly higher (relative hazard, 1.36 [CI, 0.93 to 1.99]), largely because of a nonsignificant increased incidence of ASCUS (relative hazard, 1.58 [CI, 0.99 to 2.52]).

These results suggest that cervical abnormalities are rare in postmenopausal women with previously normal Pap smears. Furthermore, the cytologic abnormalities are much more likely to be false positive than true positive, and the positive predictive value is low. The study focused on high-grade abnormalities as an end point because of the clinical importance of high-grade lesions compared with low-grade lesions. Because many low-grade cervical abnormalities will regress spontaneously, the utility of early aggressive treatment of these lesions is unclear. Treatment with oral estrogen plus progestin did not significantly affect the incidence of cytologic abnormalities.

The women in this study were at low risk for cervical cancer and had normal baseline Pap smears. These results are not generalizable to women at high risk for cervical cancer, those with a history of abnormal Pap smears, or those who have never had a Pap smear. These results support the practice of not performing cervical smears in postmenopausal women who have had a normal smear in the past 2 years. Women who choose to be screened should be informed of the likelihood of false-positive results. Although this study does not specifically address the issue of when to discontinue cervical cancer screening in postmenopausal women, these results indirectly support the U.S. Preventive Services Task Force recommendation to discontinue screening at 65 years of age in women with a history of normal cervical smears.

Sexual Dysfunction

Compared with Placebo, Transdermal Testosterone Treatment Marginally Improves Sexual Function and Psychological Well-Being in Women Who Have Had Oophorectomy

Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med. 2000;343:682-8. [PMID: 10974131]

Testosterone use in women with sexual dysfunction has received considerable media attention. However, few controlled studies have addressed its efficacy for this indication, and those that have done so used doses high enough to cause virilizing effects. The use of testosterone in women who have undergone surgical menopause is particularly compelling because testosterone levels in these women sharply decline after oophorectomy; in contrast, ovarian production of testosterone in women with natural menopause declines by only about 50%. In this manufacturer-sponsored study, Shifren and colleagues evaluated the effects of physiologic doses of transdermal testosterone in 75 healthy women who reported decreased sexual function after undergoing hysterectomy and bilateral salpingo-oophorectomy before natural menopause.

Study participants ranged in age from 31 to 56 years, were in stable monogamous relationships, had low serum total or free testosterone levels, and had lower than average scores on the Brief Index of Sexual Functioning for Women. They also reported impaired sexual function since the surgery. The investigators excluded women who were using serotonin reuptake inhibitors, had psychiatric illness, or had dyspareunia.

After a 4-week baseline period, women began three consecutive 12-week treatment periods during which they received, in random order, two placebo patches, one placebo and one active patch (150 μg/d), and two active patches (300 μg/d). All women also received a concomitant daily dose of 0.625 mg of oral conjugated equine estrogen. Outcome measures included scores on the Brief Index of Sexual Functioning for Women, the Psychological General Well-Being Index, and a sexual function diary completed daily via telephone the last 28 days of each treatment period.

Serum free testosterone level remained normal during the placebo period and increased to mid-normal and high-normal range during treatment with 150 and 300 μg of testosterone per day, respectively. The mean serum levels of total testosterone and dihydrotestosterone also increased and exceeded the respective normal ranges during treatment with 300 μg of testosterone per day.

The mean composite score on the Brief Index of Sexual Functioning for Women, expressed as a percentage of the mean value for normal women, increased from a mean (± SD) of 52% ± 27% at baseline to 72% ± 38% during the placebo period, 74% ± 37% during treatment with 150 μg of testosterone per day, and 81% ± 37% during treatment with 300 μg of testosterone per day ($P = 0.05$ for comparison with placebo).

Testosterone at 300 μg per day resulted in increased scores for frequency of sexual activity and orgasm in the Brief Index of Sexual Functioning for Women ($P = 0.03$ for both comparisons with placebo) but did not significantly affect scores on relationship satisfaction, thoughts–desire, arousal, receptivity–initiation, or problems affecting sexual function. Descriptive analyses of the frequency of sexual activity dimension of the Brief Index of Sexual Functioning showed that at the 300-μg/d dosage, the percentage of women who had sexual fantasies, masturbated, or engaged in sexual intercourse at least once a week increased two to three times from baseline. The positive well-being, depressed-mood, and composite scores of the Psychological General Well-Being Index also improved at the higher dose ($P = 0.04$, $P = 0.03$, and $P = 0.04$, respectively, compared with placebo), but the scores on the telephone-based diary did not increase significantly.

The investigators performed a post hoc analysis of the Brief Index of Sexual Functioning composite score, stratified by age, by comparing subgroups of women younger than the median age of 48 years with patients 48 years of age and older. During the placebo period, the score increased from a baseline of 50% ± 28% in the younger women to 80% ± 42%; scores did not increase further during testosterone treatment. In contrast, in the older women, the composite score increased from 53% ± 27% at baseline to 63% ± 36% during the placebo period, to 77% ± 37% with 150 μg of testosterone per day ($P = 0.03$), and to 81% ± 38% with 300 μg of testosterone per day ($P = 0.003$).

Hirsutism and acne scores, frequency of hot flashes, serum lipid levels, fasting glucose or insulin levels, and liver function test results were not significantly associated with testosterone treatment. One serious adverse event, an episode of depression, may have been related to treatment.

The researchers concluded that, in women who have undergone hysterectomy and oophorectomy and have impaired sexual function, 300 μg of transdermal testosterone per day plus oral estrogens was associated with mild improvement in sexual function (as measured by the Brief Index of Sexual Functioning for Women) and with improvements in depressed mood and positive well-being. The 150-μg/d dosage showed no benefit over placebo.

For reasons that are not clear, the benefits of transdermal testosterone were restricted to women 48 years of age and older. The study was done in a very selected population. Results are not generalizable to women who undergo natural menopause or who have coexisting conditions, such as depression or dyspareunia, that would have excluded them from this study.

The patients tolerated the treatment well in the short term. However, because the 300-μg testosterone patch resulted in a mean serum total testosterone level greater than the upper limit of normal, longer-term studies are needed to assess whether long-term daily use of the 300-μg patch is associated with clinically important androgenic effects, such as hirsutism, acne, and lipid abnormalities.

If long-term safety is established, transdermal testosterone may be appropriate treatment for selected women when it becomes commercially available. To our knowledge, no controlled trials have examined the efficacy and tolerability of the testosterone preparations currently available in the United States for this indication. The strong placebo effect found in Shifren and colleagues' study suggests that enhanced attention to impaired sexual functioning, perhaps by improving communication among couples, can alone substantially improve sexual functioning. Clinicians should be reminded to carefully assess both physical and psychosocial factors affecting sexual functioning before attempting pharmacologic interventions.

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Long-Term Medical Care of Testicular Cancer Survivors

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Testicular cancer is the most common solid tumor diagnosed in men 20 to 35 years of age. Because of highly effective treatments that may include surgery, chemotherapy, and radiation therapy, most patients become long-term survivors. Health-related issues that confront testicular cancer survivors include the late medical effects of chemotherapy, the late relapse of disease, the development of second cancers, the effect of the disease and treatment on fertility, and the psychosocial consequences. This case-based discussion focuses on the primary care physician's evaluation and management of a long-term survivor of testicular cancer who was previously treated with surgery and chemotherapy.

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A 30-year-old man presents to a general internist for evaluation. The patient states that he received curative therapy for testicular cancer at age 18. He has no other significant medical problems. He smokes one pack of cigarettes daily and drinks alcohol socially. He is married, has no children, and works as a computer programmer. He had been closely followed by his oncologist until age 24, but because of a work-related move has had no follow-up for 6 years.

WHAT DOES THE PRIMARY CARE PHYSICIAN NEED TO KNOW ABOUT THE PATIENT'S HISTORY RELATING TO TESTICULAR CANCER?

Testicular cancer is the most common solid tumor in men 20 to 35 years of age, with approximately 6900 cases diagnosed annually in the United States (1, 2). It has been described as "a model for a curable neoplasm" (3). Most patients will be cured and become long-term survivors. Many will be seen throughout their lives by primary care physicians.

The primary care physician should ask the patient about risk factors for testicular cancer, such as cryptorchidism or family history. Information on the histologic characteristics of the tumor (for example, seminoma or nonseminomatous germ-cell tumor) must also be obtained. Knowing the cancer stage at presentation is also important because prognosis and treatment are based on stage at presentation and histologic findings.

Testicular cancer may be localized (stage I) or metastatic. Testicular cancer spreads via the lymphatic system to the retroperitoneal lymph nodes (stage II). Blood-borne metastases may involve the lung and, less commonly, the liver, skeleton, and brain (stage III). Patients with metastatic disease are further classified as good risk, intermediate risk, or poor risk on the basis of defined prognostic criteria (4).

The patient had a left testicular mass at 18 years of age. Serum tumor marker assays demonstrated an α-fetoprotein level of 265 μg/mL and a human chorionic gonadotropin level of 120 IU/L. Left inguinal orchiectomy was performed. Results of pathologic testing showed a nonseminomatous germ-cell tumor. Computed tomography of the abdomen and pelvis revealed a 4-cm retroperitoneal mass. Chest radiography revealed no abnormalities. Chemotherapy consisting of three cycles of bleomycin, etoposide, and cisplatin was given. After chemotherapy, results of tumor marker assays and computed tomography were normal. The patient has been in continuous remission since the end of treatment.

WHICH THERAPIES ARE USED FOR TESTICULAR CANCER?

Radical orchiectomy is done to diagnose and treat testicular cancer. Retroperitoneal lymph node dissection results in staging and treatment in some patients with stage I and stage II nonseminomatous germ-cell tumors. Para-aortic radiation therapy may be used for seminomas, both as adjuvant therapy for stage I disease and as definitive treatment for nonbulky stage II disease. Cisplatin-based chemotherapy regimens are given to patients with metastatic disease. Other agents commonly used include etoposide and bleomycin. The risk classification system described earlier (4) determines the choice of regimen and the number of chemotherapy cycles administered. Selected patients may require postchemotherapy surgery for residual disease.

WHICH LATE TOXICITIES ARE ASSOCIATED WITH CHEMOTHERAPY FOR TESTICULAR CANCER?

For many patients with testicular cancer, cisplatin-based chemotherapy is critical for cure. However, this

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Table 1. **Screening and Intervention for Potential Late Effects of Cisplatin-Based Chemotherapy in Testicular Cancer Survivors**

Late Effect	Screening Approach	Intervention
Vascular		
Raynaud phenomenon	History	Behavior modification
Hyperlipidemia	Lipid profile	Diet, exercise, and medication
Hypertension	Blood pressure	Diet, exercise, and medication
Renal		
Impaired glomerular filtration rate	Serum creatinine level	Treat hypertension; avoid nephrotoxins
Hypomagnesemia	Serum magnesium level	Supplemental magnesium
Increased plasma renin and aldosterone levels	Blood pressure	Diet, exercise, and medication
Otologic		
Tinnitus and hearing loss	History; audiogram if otologic effect suspected	Avoid noise; refer to specialist
Neurologic		
Peripheral neuropathy	History; neurologic examination	Behavior modification; avoid neuropathic agents
Reproductive		
Impaired spermatogenesis	Semen analysis	Pretreatment sperm banking; in vivo or in vitro fertilization; testicular sperm extraction

therapy may be associated with long-term consequences that may affect several organ systems (**Table 1**) (5–11). A recent study showed that circulating plasma levels of cisplatin may be detectable for up to 20 years after treatment (12). The development of late consequences related to cisplatin-based chemotherapy is not specific to patients with testicular cancer but must be considered because of the high proportion of these patients who will become long-term survivors.

Chemotherapy for testicular cancer is associated with vascular toxicity. The reported incidence of Raynaud phenomenon in patients with testicular cancer treated with cisplatin-based chemotherapy ranges from 10% to 49% (6, 8, 9, 13). Bleomycin is largely responsible for these symptoms. In up to half of patients, symptoms will gradually resolve. Serious vascular complications, including myocardial infarction, stroke, and thromboembolic disease, have been reported in men with testicular cancer treated with cisplatin-based chemotherapy (14–16).

In a study of patients with testicular cancer who were treated with surgery or with surgery and cisplatin-based chemotherapy, Nichols and colleagues (17) reported no increased risk for cardiovascular events in the chemotherapy group at a median follow-up of 5 years. More recently, Meinardi and coworkers (18) demonstrated an observed-to-expected ratio of cardiovascular events of 7.1 (95% CI, 1.9 to 18.3) for patients with testicular cancer who were age 50 years or younger, had received chemotherapy, and were in remission for 10 or more years compared with a general male population. The potential increased risk for cardiovascular events can be explained, in part, by studies that demonstrated the development of hypertension and hyperlipidemia after chemotherapy in these patients (9, 18–21). Increased risk could also be related to cisplatin-mediated vascular endothelial injury (11). Additional studies are needed to define the actual risk, if any, for early cardiovascular events in long-term survivors of testicular cancer who received chemotherapy. We recommend that the primary care physician be attentive to identifying and treating modifiable cardiovascular risk factors, including tobacco use, hypertension, and hyperlipidemia, in these patients.

Some degree of nephrotoxicity occurs in all patients who receive cisplatin (5–7, 9–11, 22, 23). The decrease in glomerular filtration rate may not improve over time (5–7, 9, 22, 23). Although this decreased glomerular filtration rate may not have immediate clinical relevance, its potential effect on long-term renal function and associated conditions is not clear (18). Cisplatin also results in hypomagnesemia and increased plasma renin and aldosterone levels (9, 24, 25), which may contribute to cardiovascular toxicity. We recommend that primary care physicians monitor magnesium levels because chronic magnesium wasting can occur for many years in some patients.

Tinnitus and high-frequency hearing loss (4 to 8 MHz) are persistent problems in approximately 20% of patients treated with cisplatin-based chemotherapy for testicular cancer (7, 9, 26). Possible risk factors for ototoxicity include cumulative cisplatin dose, history of noise exposure, and preexisting hearing loss (26).

Peripheral neuropathy, typically sensory, may occur after cisplatin-based chemotherapy. Most of the reported cases of substantial neurotoxicity have resulted from the cisplatin, vinblastine, and bleomycin regimen, which currently is not standard therapy (27). Substituting etoposide for vinblastine has dramatically decreased the incidence of neuropathy (28).

Acute pulmonary toxicity secondary to bleomycin is a rare but well-known complication (29). Cigarette smoking has been identified as a risk factor for bleomycin-induced pulmonary toxicity (6, 11, 30). Long-term pulmonary function is preserved in most testicular cancer survivors, even if bleomycin was administered (31).

IF CHEMOTHERAPY-RELATED LATE TOXICITY IS IDENTIFIED, WHICH INTERVENTIONS SHOULD BE CONSIDERED?

Interventions should be based on the seriousness of the late effects. If the patient reports the Raynaud phenomenon or paresthesia, the physician can encourage the patient to modify any behavior that worsens the symptoms. Hypertension and lipid abnormalities can be addressed with dietary modification, exercise, and medications, as indicated. Renal function may be preserved over the long term by controlling hypertension and diabetes, if they are present, and by avoiding unnecessary exposure to nephrotoxic agents. Although the effect of ongoing smoking on pulmonary function in the bleomycin-exposed lung has not been defined, the cardiovascular and carcinogenic effects of smoking are well known. Patients should be strongly encouraged to stop smoking and offered the opportunity to participate in smoking cessation programs. The physician should ask about noise exposure in the workplace to potentially limit additional hearing loss. Patients in whom cisplatin-induced ototoxicity is suspected should be referred for audiologic examination; most, however, will not need corrective hearing devices (26).

The patient admits that his digits become discolored and uncomfortable when exposed to severe cold. Although mild, these symptoms are annoying. He has a dry cough that he attributes to smoking, but no dyspnea. He reports no hearing loss or tinnitus. The primary care physician counsels the patient on ways to avoid cold exposure, strongly recommends discontinuing tobacco use, and refers the patient to a smoking cessation program.

The physician then begins to examine the patient.

WHICH ASPECTS OF PHYSICAL EXAMINATION ARE IMPORTANT FOR TESTICULAR CANCER SURVIVORS?

The physician caring for the testicular cancer survivor should perform a complete physical examination annually. Weight and blood pressure should be recorded. The skin should be examined for pigmented lesions because patients with testicular cancer appear to have an increased risk for dysplastic nevi (32, 33). The lymph node examination is important because recurrence can sometimes be detected in the neck. The remaining testicle should be examined because of the increased risk for developing a second germ-cell tumor (34, 35).

ARE LABORATORY TESTS INDICATED?

We recommend performing serum tumor marker assays (α-fetoprotein and human chorionic gonadotropin) and chest radiography annually to monitor for disease recurrence. For patients who received chemotherapy, renal function should be assessed at baseline by measuring serum creatinine and magnesium concentrations. In addition, we recommend that all patients, starting 2 years from the end of chemotherapy, have a baseline lipid analysis with subsequent testing as indicated.

On physical examination, the patient's blood pressure is 135/90 mm Hg and his heart rate is 72 beats/min. A skin examination reveals scattered nevi across the trunk, one of which is 6 mm in diameter with irregular borders. The remainder of the physical examination is normal. The remaining testicle is normal.

The patient is especially concerned about the risk for developing cancer later in life. He asks the physician for comprehensive cancer screening and for measures he can take to prevent the development of another cancer.

WHAT ARE THE RISKS FOR LATE RELAPSE OF TESTICULAR CANCER AND FOR SECOND TESTICULAR CANCER?

For patients with testicular cancer, most recurrences occur within 2 years of the end of treatment. However, late recurrence of testicular cancer may occur in both early- and advanced-stage disease (36–38). The incidence of late relapse is approximately 2% to 3%. The most common sites of late recurrence are the retroperitoneum and chest. Late recurrences are primarily managed with surgery because they are often refractory to chemotherapy. Because of the possibility of late recurrence, patients with testicular cancer need lifelong monitoring.

Three percent to 4% of patients with a history of testicular cancer will develop a second testicular cancer, and the increased risk levels off 15 to 20 years after the initial diagnosis (34–35). This observation may, in part, result from an increased incidence of carcinoma in situ in the contralateral testis, a known precursor to germ-cell tumors (39). Chemotherapy may decrease the risk for or postpone the development of carcinoma in situ and subsequent testicular cancer (40). Patients who undergo a second orchiectomy will require long-term testosterone replacement therapy. The identification of bilateral testicular cancer may signify a genetic susceptibility to the disease. Recently, genetic linkage analysis of families with multiple cases of testicular cancer (including bilateral cancer) has led to identification of a testicular cancer susceptibility gene locus that is mapped to chromosome Xq27 (41).

HOW SHOULD THE PHYSICIAN LOOK FOR RECURRENT TESTICULAR CANCER?

The physician overseeing the long-term care of testicular cancer survivors should annually perform a complete physical examination that includes careful assessment of the remaining testicle. As noted previously, annual studies, including serum tumor marker assays and chest radiography, should be performed to screen for disease recurrence. Additional radiologic studies, such as testicular ultrasonography or computed tomography of the retroperitoneum, should be performed if recurrent disease is suspected.

ARE PATIENTS WHO SURVIVE TESTICULAR CANCER AT SUBSEQUENT RISK FOR DEVELOPING OTHER CANCERS?

Patients cured of testicular cancer have been shown to be at risk for the development of cancer later in life. In an analysis of 16 population-based cancer registries in North America and Europe, which included 28 843 patients treated for germ-cell tumors between 1935 and 1993, the observed-to-expected ratio of second cancers in this population compared to the general population was 1.43 (CI, 1.36 to 1.51) (42). These second cancers included both radiation-induced solid tumors and chemotherapy-induced leukemia. Many patients treated in this series received outdated treatments that were probably more carcinogenic than are current treatments. In patients with testicular cancer treated more recently, the risk for a second cancer may be substantially lower.

For testicular cancer survivors who have received radiation therapy, the overall risk for developing a secondary solid tumor is approximately two to three times greater than that of like-aged persons in the general population. The risk for developing a secondary solid tumor increases in proportion to the duration of follow up. Solid tumors that have been identified include sarcomas and cancers of the gastrointestinal and genitourinary tract (42–46). Acute myelogenous leukemia with specific abnormalities in chromosome 11q23 may occur 2 to 3 years after treatment with etoposide (45–49). The risk for leukemia appears to be cumulative and dose-dependent. At standard doses of etoposide (≤ 2 g/m^2, the total cumulative dose for up to four cycles of either the bleomycin, etoposide, and cisplatin or the etoposide and cisplatin regimen), the overall incidence of leukemia is expected to be very low ($<0.5\%$). However, at higher doses of etoposide (>2 g/m^2), the 5-year incidence increases to about 2% (46, 47).

An association has been reported between testicular cancer and dysplastic nevi (32, 33). Dysplastic nevi may be precursors to melanoma. One study demonstrated that 37% of patients with germ-cell tumors had multiple, atypical nevi as compared with 15% of healthy controls (33). An increased incidence of melanoma has also been reported in survivors of germ-cell tumors (42, 50). It is not known whether these patients have an inherent increased risk for dysplastic nevi or whether treatment plays a role. We recommend that patients with testicular cancer who have atypical nevi be referred to a dermatologist for careful skin assessment and surveillance.

WHAT CAN PATIENTS DO TO DECREASE THE RISK FOR SECOND CANCERS?

It is not known whether second cancers can be prevented in testicular cancer survivors. However, certain measures may be helpful. Patients should be instructed and encouraged to self-examine the remaining testicle and skin regularly. In addition, patients should be vigorously encouraged to refrain from or discontinue smoking. Limiting sun exposure and using sunscreens should also be encouraged. Finally, early detection of common types of cancer, such as colorectal and prostate cancer, should be addressed at the appropriate age.

The patient mentions that he and his wife have been trying to have a child, but his wife has not yet become pregnant. The patient reports that he banked his sperm before receiving chemotherapy. He notes that his erectile and ejaculatory functions are normal.

WHAT IS THE LIKELIHOOD THAT THE PATIENT HAS DECREASED FERTILITY?

In newly diagnosed patients, decreased spermatogenesis and increased levels of follicle-stimulating hormone may be observed before orchiectomy (51, 52). Approximately one third of patients who have undergone orchiectomy have severe oligospermia or azoospermia (53). Cisplatin-based chemotherapy also substantially impairs spermatogenesis (54–58). The probability for recovery of spermatogenesis after chemotherapy depends on the age of the patient, the severity of pretreatment oligospermia, and the cumulative dose of chemotherapy received (54, 59). Some patients with oligospermia can still father children (57). Chemotherapy may also result in Leydig-cell dysfunction, which increases luteinizing hormone levels. Serum testosterone levels remain in the normal range in most patients (60–63). Patients who undergo retroperitoneal lymph node dissection may develop dry ejaculation. The introduction of nerve-sparing surgery has preserved normal ejaculation in most men who undergo this procedure (64–66).

ARE THERE INTERVENTIONS TO IMPROVE FERTILITY IN PATIENTS TREATED FOR TESTICULAR CANCER?

Patients with testicular cancer who will have retroperitoneal lymph node dissection or chemotherapy should be encouraged to bank sperm before having these treatments (67). If fertility is an important concern, infertile testicular cancer survivors should be referred to a center specializing in assisted reproductive technologies. In vitro and in vivo fertilization using banked sperm is usually successful. Recent technical advances, such as intracytoplasmic sperm injection, offer survivors additional hope of paternity. Finally, sperm have been successfully extracted from testicular tissue in patients with chemotherapy-related, nonobstructive azoospermia (67, 68).

The patient's affect seems flat. He states that he is pleased with his marriage but worries about whether he and his wife will ever be able to have children.

ARE CERTAIN MENTAL HEALTH PROBLEMS PREVALENT IN TESTICULAR CANCER SURVIVORS? IS FORMAL PSYCHOLOGICAL TESTING INDICATED?

Studies have demonstrated that fewer than 10% of testicular cancer survivors are affected by long-term psychosocial consequences (69–74). In one study, the health-related quality of life in long-term testicular cancer survivors was reported to be as good as or even better than that of men in the general population (69). Studies have demonstrated that sexual function and fertility are important predictors of psychosocial outcome (74–77). Testicular cancer survivors may report concerns about sexuality, such as decreased libido, diminished orgasm intensity, and erectile or ejaculatory impairment (75–82). Potential sexual problems should be discussed with patients before commencing cancer treatment and at follow-up visits (83, 84). Because the minority of testicular cancer survivors suffer long-term psychological distress, we do not advocate formal psychological evaluation and testing unless psychosocial concerns are suspected.

The patient asks whether he should see an oncologist at this point. He also wonders how frequently he should see his primary care physician for follow-up.

HOW OFTEN SHOULD THE PRIMARY CARE PHYSICIAN SEE THE PATIENT FOR ROUTINE FOLLOW-UP? WHICH TESTS SHOULD BE DONE AT THESE VISITS? WHEN SHOULD THE PATIENT BE REFERRED TO A CANCER SPECIALIST?

At the end of treatment, most patients with testicular cancer begin a follow-up schedule with a cancer specialist to monitor for disease recurrence. Visits are usually more frequent during the first 2 years after treatment and become less frequent between years 3 and 5. After year 5, patients should be seen annually by a cancer specialist for detection of late recurrence. We also recommend that testicular cancer survivors who are more than 2 years from the

Table 2. **Recommendations for the Annual Medical Evaluation of Testicular Cancer Survivors***

Recommendation	Rationale (Reference)
Complete history with special attention to	
Tobacco use	Cardiovascular and carcinogenic risks
Sunscreen use	Increased risk for dysplastic nevi (32, 33)
Fertility assessment	Potential for subfertility associated with the disease and treatment
Psychosocial and sexuality status	Interrelationship between sexuality and psychosocial status (74–77)
Cardiovascular risk factors associated with cisplatin-based chemotherapy	Postchemotherapy hypertension and hyperlipidemia (9, 18–21)
Late effects of cisplatin-based chemotherapy	Impact on multiple organ systems
Complete physical examination, including	
Blood pressure	Postchemotherapy hypertension (9, 18, 19)
Skin examination	Increased risk for dysplastic nevi (32, 33)
Testis examination	3%–4% risk for secondary germ-cell tumor (34, 35)
Laboratory monitoring	
Serum tumor marker assays	2%–3% risk for late relapse (36–38)
Serum creatinine and magnesium associated with cisplatin-based chemotherapy	Decreased glomerular filtration rate and hypomagnesemia (5–7, 9, 22–25)
Lipid profile associated with cisplatin-based chemotherapy	Postchemotherapy hyperlipidemia (9, 18–21)
Radiologic studies	
Chest radiography	2%–3% risk for late relapse (36–38)

* These recommendations are the opinions of the authors and have not undergone consensus review or prospective validation.

completion of treatment have annual comprehensive medical evaluations. Either a primary care physician with knowledge of testicular cancer and treatment sequelae or a cancer specialist with expertise in general medicine should perform this medical evaluation. The visit should center on an assessment of the patient's overall health status, with special focus on the potential late consequences of testicular cancer and its treatment. Our recommendations for the annual medical evaluation of testicular cancer survivors are summarized in Table 2. Primary care physicians should refer patients to a cancer specialist if disease recurrence is suspected. With careful attention to the medical and psychosocial issues that confront testicular cancer survivors, informed primary care physicians can have an important effect on the long-term well-being of these patients.

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Deconstructing the Placebo Effect and Finding the Meaning Response

Daniel E. Moerman, PhD, and Wayne B. Jonas, MD

We provide a new perspective with which to understand what for a half century has been known as the "placebo effect." We argue that, as currently used, the concept includes much that has nothing to do with placebos, confusing the most interesting and important aspects of the phenomenon. We propose a new way to understand those aspects of medical care, plus a broad range of additional human experiences, by focusing on the idea of "meaning," to which people, when they are sick, often respond. We review several of the many areas in medicine in which meaning affects illness or healing and introduce the idea of the "meaning response." We suggest that use of this formulation, rather than the fixation on inert placebos, will probably lead to far greater insight into how treatment works and perhaps to real improvements in human well-being.

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> [The cure for the headache] was a kind of leaf, which required to be accompanied by a charm, and if a person would repeat the charm at the same time that he used the cure, he would be made whole; but that without the charm the leaf would be of no avail."
>
> —*Socrates, according to Plato (1)*

There is a renewed interest in placebos and the placebo effect—on their reality, their ethics, their place in medicine, or not, both in and out of the clinic and academy. The U.S. National Institutes of Health recently sponsored a large conference called "Science of the Placebo" (2). At least five serious books on the subject (3–7) plus a book of poetry (8) and a novel (9)—each titled *Placebo Effect*—have been published since 1997. In the past 10 years, the National Library of Medicine has annually listed an average of 3972 scholarly papers with the keywords "placebo," "placebos," or "placebo effect," with a low of 3362 papers in 1992 and a high of 4814 in 2000. During the fall of 2000, a discussion of the effect of new "drag free" suits, which might give an edge to Olympic swimmers, appeared in *US News and World Report*: "[S]wimming officials aren't convinced this is anything more than the placebo effect. Swimmers excel because they *think* they've got an edge" (10). One widely reported study, which concluded that placebos were powerless (11), or represented the Wizard of Oz (12), occasioned a blizzard of criticism (13–26) and some support (27). It's in the papers (28, 29). It's in the air.

Yet the most recent serious attempt to try logically to define the placebo effect failed utterly (30). Given the ways people have gone about it, this seems unsurprising. Arthur K. Shapiro, MD, who spent much of his career as a psychiatrist studying the placebo effect, recently wrote:

> A placebo is a substance or procedure . . . that is objectively without specific activity for the condition being treated . . . The placebo effect is the . . . therapeutic effect produced by a placebo. (31)

If we replace the word "placebo" in the second sentence with its definition from the first, we get: "The placebo effect is the therapeutic effect produced by [things] objectively without specific activity for the condition being treated." This makes no sense whatsoever. Indeed, it flies in the face of the obvious. The one thing of which we can be absolutely certain is that placebos *do not* cause placebo effects. Placebos are inert and don't cause anything.

Moreover, people frequently expand the concept of the placebo effect very broadly to include just about every conceivable sort of beneficial biological, social, or human interaction that doesn't involve some drug well-known to the pharmacopoeia. A narrower form of this expansion includes identifying "natural history" or "regression to the mean" (as we might observe them in a randomized, controlled trial) as part of the placebo effect. But natural history and regression occur not only in the control group. Nothing in the theory of regression to the mean (31) hints that when people are selected for being extreme on some measure (blood pressure or cholesterol, for example), they are immune to regression if they receive active treatment. Such recipients are as

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likely (or unlikely) to move toward homeostasis as are control group patients. So, regression to the mean is in no meaningful way a "placebo effect." Ernst and Resch (32) took an important step in trying to clarify this situation by differentiating the "true" from the "perceived" placebo effect. But "true placebo effect" hasn't really caught on as a viable concept.

The concept of the placebo effect has been expanded much more broadly than this. Some attribute the effects of various alternative medical systems, such as homeopathy (33) or chiropractic (34), to the placebo effect. Others have described studies that show the positive effects of enhanced communication, such as Egbert's (35), as "the placebo response without the placebo" (7).

No wonder things are confusing.

MEANING AND MEDICINE

We suggest thinking about this issue in a new way. A group of medical students was asked to participate in a study of two new drugs, one a tranquilizer and the other a stimulant (36). Each student was given a packet containing either one or two blue or red tablets; the tablets were inert. The students' responses to a questionnaire indicated that 1) the red tablets acted as stimulants while the blue ones acted as depressants and 2) two tablets had more effect than one. The students were not responding to the inertness of the tablets. Moreover, these responses cannot be easily accounted for by natural history, regression to the mean, or physician enthusiasm (presumably the experimenters were as enthusiastic about the reds as the blues). Instead, they can be explained by the "meanings" in the experiment: 1) Red means "up," "hot," "danger," while blue means "down," "cool," "quiet" and 2) two means more than one. These effects of color (37–40) and number (41, 42) have been widely replicated.

In a British study, 835 women who regularly used analgesics for headache were randomly assigned to one of four groups (43). One group received aspirin labeled with a widely advertised brand name ("one of the most popular" analgesics in the United Kingdom that had been "widely available for many years and supported by extensive advertising"). The other groups received the same aspirin in a plain package, placebo marked with the same widely advertised brand name, or unmarked placebo. In this study, branded aspirin worked better than unbranded aspirin, which worked better than branded placebo, which worked better than unbranded placebo. Among 435 headaches reported by branded placebo users, 64% were reported as improved 1 hour after pill administration compared with only 45% of the 410 headaches reported as improved among the unbranded placebo users. Aspirin relieves headaches, but so does the knowledge that the pills you are taking are "good" ones.

In a study of the benefits of aerobic exercise, two groups participated in a 10-week exercise program. One group was told that the exercise would enhance their aerobic capacity, while the other group was told that the exercise would enhance aerobic capacity and psychological well-being. Both groups improved their aerobic capacity, but only the second group improved in psychological well-being (actually "self-esteem"). The researchers called this "strong evidence . . . that exercise may enhance psychological well-being via a strong placebo effect" (44).

In the red versus blue pill study, we can correctly (if not very helpfully) classify the responses of the students as "placebo effects" because they did indeed receive inert tablets; it seems clear, however, that they responded not to the pills but to their colors. In the second study, the presence of the brand name enhanced the effect of both the inert and the active drug. It doesn't seem reasonable to classify the "brand name effect" as a "placebo effect" because no placebos are necessarily involved. Meanwhile, calling the consequences of authoritative instruction to the exercisers a "placebo effect" could come only from someone who believes that words do not affect the world, someone who has never been told "I love you" or who has never read the reviews of a rejected grant proposal. It seems reasonable to label all these effects (except, of course, of the aspirin and the exercise) as "meaning responses," a term that seeks, among other things, to recall Dr. Herbert Benson's "relaxation response" (45). Ironically, although placebos clearly cannot do anything themselves, their meaning can.

We define the *meaning response* as the physiologic or psychological effects of meaning in the origins or treatment of illness; meaning responses elicited after the use of inert or sham treatment can be called the "placebo effect" when they are desirable and the "nocebo effect" (46) when they are undesirable. This is obviously a complex notion with several terms that would be challenging to unpack ("desirable," "effect," "meaning," "treatment," "illness")—an exercise that cannot be carried out here. Note that this definition excludes several elements that are usually included in our understanding of the placebo effect, such as natural history, regression, experimenter or subject bias, and error in measurement or reporting. Note as well that the definition is not phrased in terms of "nonspecific" effects; although many elements of the meaning response or placebo effect may seem nonspecific, they are often quite specific in principle after they are understood.

Meaning Permeates Medical Treatment

Insofar as medicine is meaningful, it can affect patients, and it can affect the outcome of treatment (47–49). Most elements of medicine *are* meaningful, even if practitioners do not intend them to be so. The physician's costume (the white coat with stethoscope hanging out of the pocket) (50), manner (enthusiastic or not), style (therapeutic or experimental), and language (51) are all meaningful and can be shown to affect the outcome; indeed, we argue that both diagnosis (52) and prognosis (53) can be important forms of treatment.

Many studies can be cited to document aspects of the therapeutic quality of the practitioner's manner (54). In one, a strong message of the effect of a drug (an inert capsule) substantially reduced the patients' report of the pain of mandibular block injection compared with the pain after a weak message. Patients who received the weak message reported less pain than a group that received no placebos and no message at all (55). In another study, 200 patients with symptoms but no abnormal physical signs were randomly assigned to a positive or a negative consultation. In a survey of patients 2 weeks later, 64% of patients in the positive consultation group said they were all better, while only 39% of those who had negative consultations thought they were better (56).

Although there is strong evidence for such "physician effects," little evidence shows that "patient effects" are very important. A mass of research in the 1970s designed to identify "placebo reactors" produced only inconsistent and contradictory findings (57–59).

Meaning Can Have Substantial Physiologic Action

Placebo analgesia can elicit the production of endogenous opiates. Analgesia elicited with an injection of saline solution can be reversed with the opiate antagonist naloxone and enhanced with the opiate agonist proglumide (60). Likewise, acupuncture analgesia can be reversed with naloxone in animals (61) and people (62). To say that a treatment such as acupuncture "isn't better than placebo" does not mean that it does nothing.

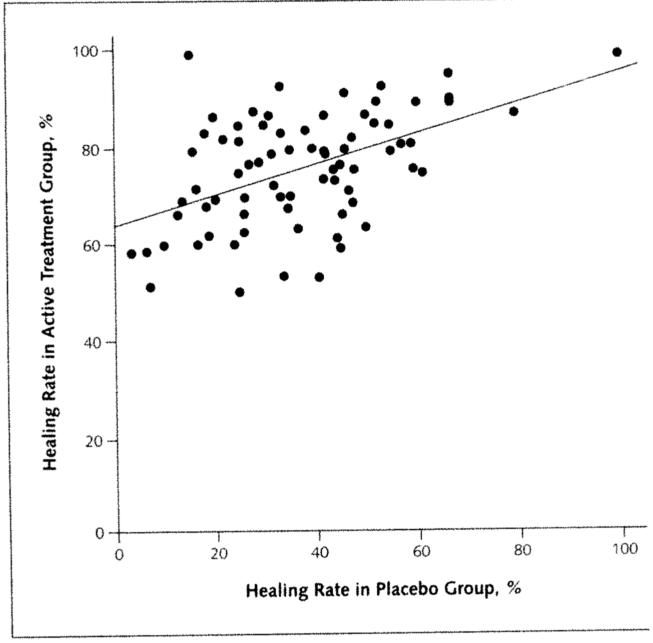
Meaning and Surgery

The classic example of the meaningful effects of surgery comes from two studies of ligation of the bilateral internal mammary arteries as a treatment for angina (63, 64). Patients receiving sham surgery did as well—with 80% of patients substantially improving—as those receiving the active procedure in the trials or in general practice. Although the studies were small, the procedure was no longer performed after these reports were published. Of note, these effectiveness rates (and those reported by the proponents of the procedure at the time) are much the same as those achieved by contemporary treatments such as coronary artery bypass or β-blockers.

Some observers have suggested that the success of transmyocardial laser revascularization, a procedure without a clear mechanism, may be explained by what they call the placebo effect (65) but what we call the meaning response. This is a plausible interpretation of a recent trial showing dramatic improvement in very sick people in both participant groups of a control trial of transmyocardial laser revascularization (Leon MB, Baim DS, Moses JW, Laham RJ, Knopf W. A randomized blinded clinical trial comparing percutaneous laser myocardial revascularization [using Biosense LV Mapping] vs. placebo in patients with refractory coronary ischemia. Presented at American Heart Association Scientific Session, 12–15 November 2000).

Surgery is particularly meaningful: Surgeons are among the elite of medical practitioners; the shedding of blood is inevitably meaningful in and of itself. In addition, surgical procedures usually have compelling rational explanations, which drug treatments often do not. The logic of arthroscopic surgery ("we will clean up a messy joint") is much more sensible and understandable (and even effective [66]), especially for people in a culture rich in machines and tools, than is the logic of nonsteroidal anti-inflammatory drugs (which "inhibit the production of prostaglandins which are involved in the inflammatory process," something no one would ever tell a patient). Surgery clearly induces a profound meaning response in modern medical practice (67–69).

Figure. **Data from 83 studies of the use of cimetidine or ranitidine for duodenal ulcer disease.**



In all cases, ulcers and ulcer healing were diagnosed endoscopically. Most studies lasted 4 weeks; a few were a bit shorter or longer. Sample sizes ranged from 12 to 210 participants (mean, 58). The quality of these studies was generally good for the era in which they were conducted (mostly between 1976 and 1986), although probably not fully adequate by contemporary standards. This analysis differs from the ordinary, in which placebo and active treatments are combined in an odds ratio, relative risk, or risk difference. The point of this analysis is not, however, to determine whether antisecretory medication is effective; clearly it is. The issue is the relationship between the pharmacologic and the meaningful dimensions of treatment. (A detailed account of these studies is available elsewhere [42].)

MEANING, CULTURE, AND MEDICINE

Anthropologists understand cultures as complex webs of meaning, rich skeins of connected understandings, metaphors, and signs. Insofar as 1) meaning has biological consequence and 2) meanings vary across cultures, we can anticipate that biology will differ in different places, not because of genetics but because of these entangled ideas; we can anticipate what Margaret Lock has called "local biologies" (70, 71); Lock has shown dramatic cross-cultural variation in the existence and experience of "menopause" (70, 71). Moreover, Phillips has shown that "Chinese Americans, but not whites, die significantly earlier than normal (1.3 to 4.9 y) if they have a combination of disease and birth year which Chinese astrology and medicine consider ill fated" (72). Among Chinese Americans whose deaths were attributed to lymphatic cancer ($n = 3041$), those who were born in "Earth years"—and consequently were deemed by Chinese medical theory to be especially susceptible to diseases involving lumps, nodules, or tumors—had an average age at death of 59.7 years. In contrast, among those born in other years, age at death of Chinese Americans with lymphatic cancer was 63.6 years—nearly 4 years longer. Similar differences were also found for various other serious diseases. No such differences were evident in a large series of "whites" who died of similar causes in the same period. The intensity of the effect was shown to be correlated with "the strength of commitment to traditional Chinese culture." These differences in longevity (up to 6% or 7% difference in length of life!) are not due to having Chinese genes but to having Chinese ideas, to knowing the world in Chinese ways. The effects of meaning on health and disease are not restricted to placebos or brand names but permeate life.

One of us has shown variation in the response of control groups to inert medication in diverse cultures for the same conditions (ulcers, hypertension, and anxiety) (42). The **Figure** shows the relationship between control group and active treatment group healing for endoscopically diagnosed duodenal ulcer treated with antisecretory medication. Control group healing and active treatment group healing seem functionally related in these studies. The correlation between control and active healing rates is 0.49; as the placebo group's healing rate increases, so does the rate of the active treatment group. Although the average control group healing rate in five German studies has been 62.4%, the healing rate was 16.7% in three studies from neighboring Denmark and the Netherlands. The number needed to treat for benefit (NNT_B), to obtain ulcer healing, can be calculated; for ulcer patients treated with placebo, the NNT_B for those who are German (not Danish or Dutch) is 2.

CONCLUSIONS

Practitioners can benefit clinically by conceptualizing this issue in terms of the meaning response rather than the placebo effect. Placebos are inert. You can't do anything about them. For human beings, meaning is everything that placebos are not, richly alive and powerful. However, we know little of this power, although all clinicians have experienced it. One reason we are so ignorant is that, by focusing on placebos, we constantly have to address the moral and ethical issues of prescribing inert treatments (73, 74), of lying (75), and the like. It seems possible to evade the entire issue by simply avoiding placebos. One cannot, however, avoid meaning while engaging human beings. Even the most distant objects—the planet Venus, the stars in the constellation Orion—are meaningful to us, as well as to others (76).

Yet, a huge puzzle remains: Obviously the meaning response is of great value to the sick and the lame. For example, eliciting the meaning response requires remarkably little effort ("You will be fine, Mr. Smith"). So why doesn't this happen all the time? And why can't you do it to yourself? Psychologist Nicholas Humphrey has suggested that this conundrum may have evolutionary roots: Healing has its benefits but also its costs (77). (For example, relieving pain may encourage premature activity, which could exacerbate the injury. Moreover, immune activity is metabolically very demanding on an injured system.) Perhaps only when a friend, relative, or healer indicates some level of social support (for example, by performing a ritual) is the individual's internal economy able to act. Moreover, as we have clarified, routinized, and rationalized our medicine, thereby relying on the salicylates and forgetting about the more meaningful birches, willows, and wintergreen from which they came—in essence, stripping away Plato's "charms"—we have impoverished the meaning of our medicine to a degree that it simply doesn't work as well as it might any more. Interesting ideas such as this are impossible to entertain when we discuss placebos; they spring readily to mind when we talk about meaning.

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EDITORIAL

Recognition and Treatment of Erythema Migrans: Are We Off Target?

The clinical manifestation most closely associated with Lyme disease is the rash that develops at the site of a bite from an *Ixodes scapularis* tick. Erythema migrans is present in at least 90% of objective cases of Lyme disease (1). Although it usually resolves spontaneously (that is, without any antimicrobial therapy), it may be the forerunner, in untreated patients, of cardiac, neurologic, or arthritic conditions, causing significant morbidity (1, 2). These sequelae generally respond to antibiotics (1–3). However, treatment of patients with erythema migrans is usually highly effective in preventing the development of these complications (1–3).

Despite the importance of erythema migrans, its clinical diagnosis has not been completely straightforward. Although once considered pathognomonic for Lyme disease, erythema migrans may be confused with other rashes that are virtually identical in appearance. These include a localized inflammatory reaction that may follow an arthropod bite but is unassociated with *Borrelia burgdorferi* infection (4, 5), and a recently described rash linked to the bite of an *Amblyomma* tick and a separate etiologic agent (6). In practice, erythema migrans has been diagnosed primarily on clinical grounds, without laboratory testing. However, microbiological confirmation is useful in a research setting to distinguish definite cases of Lyme disease and to define the true clinical features (7, 8). Recovery of *B. burgdorferi* from cultures of skin biopsy specimens or blood is the gold standard for diagnosis of early Lyme disease.

In this issue, Smith and colleagues (9) describe the clinical manifestations of illness and outcome in a group of U.S. patients with erythema migrans and laboratory evidence of *B. burgdorferi* infection. All patients were part of a larger cohort of nearly 11 000 participants who had initially enrolled in a double-blind, placebo-controlled study of the safety and efficacy of a Lyme disease vaccine. Smith and colleagues reviewed data from 118 patients whose *B. burgdorferi* infection was confirmed by a positive culture or positive results on polymerase chain reaction (PCR). For 12% of patients with negative cultures, the microbiological diagnosis was supported by PCR alone. Given the risks for false-positive results on PCR, diagnosis was necessarily somewhat less definite for these patients than for patients with positive cultures.

The greatest strength of the study was the broad geographical representation of patients. Forty-seven percent were from New England, 51% were from mid-Atlantic states, and 2% were from Wisconsin. Thus, these findings might be generalizable to endemic areas in the eastern United States.

Participants in the Smith study were somewhat less ill than those in most other U.S. studies of Lyme disease. Only 57% of Smith and colleagues' patients had systemic manifestations, compared with approximately 75% of patients in previous reports (7, 8, 10, 11). Only 7% had erythema migrans at multiple sites, a manifestation of hematogenous dissemination, in contrast to approximately 15% of patients in other recent U.S. studies (7, 8, 10, 12). This is probably because patients in the Smith study were seen earlier in the course of their illness (median, 3 days) as part of a successful concerted effort to evaluate ill patients promptly in the vaccine efficacy trial. It might therefore be argued that Smith and colleagues' patients are not completely representative of those seen by most U.S. clinicians. However, many clinical findings in their study were similar to those reported previously; fever, headache, and musculoskeletal findings predominated, and respiratory and gastrointestinal symptoms were uncommon (7, 8, 10–12).

A key finding may surprise many readers. Smith and colleagues report that in most cases in the United States, erythema migrans is not shaped like a bull's-eye or a target. This important finding confirms the results of previous investigation in a single region of New York State (7, 8). Many patients and clinicians in endemic areas do not even consider the possibility of Lyme disease if a rash does not have "classic" central clearing. On the other hand, patients who develop small bull's-eye lesions (dime- to quarter-size) after arthropod bites have only local inflammation, not *B. burgdorferi* infection, and should not be treated with antibiotics. In the study by Smith and colleagues (9) and in two other recent U.S. reports (7, 8), erythema migrans tended to lack a target-like appearance because central clearing develops as a function of rash duration (7, 8, 13) and patients now present sooner than they did previously. Similarly, in European series (8, 13), erythema migrans demonstrated central clearing because the rashes were present longer than those in more recent U.S. studies (7, 8, 10).

As in most other series of patients with erythema migrans, objective evidence of treatment failure was extremely rare (1 patient developed an unexplained small, transient knee effusion but had negative results on serologic tests, and therefore probably did not have Lyme arthritis). Thirteen patients (11%) experienced persistent signs or symptoms after treatment, similar to reported rates of subjective symptoms in treatment trials for early Lyme disease (10, 12). Conclusions about outcome, however, must be tempered by the lack of standardization in patient evaluations and treatment.

Perhaps the most striking feature of patient management was the wide variety of treatment regimens used by study practitioners. The median duration of therapy was more than 3 weeks, and patients who received amoxicillin were treated for a median of 30 days. The wide variation in treatment duration is not unique to the present study and is unjustified. The Infectious Diseases Society of America recently issued evidence-based guidelines recommending 14 to 21 days of an oral antibiotic (usually doxycycline or amoxicillin) for the treatment of erythema migrans (3). There has been a trend toward longer courses of antibiotics in recent years, in the absence of new treatment trials evaluating duration of therapy. In fact, the only two published U.S. studies to address the issue of length of therapy for erythema migrans found no difference between 10 days and 20 days of tetracycline (14) or 14 days and 21 days of doxycycline (15). Preliminary information from a prospective, double-blind, placebo-controlled study indicated that patients randomly assigned to receive 10 or 20 days of oral doxycycline had equally good outcome over prolonged follow-up (30 months) (16).

The reasons for the trend toward longer therapy for erythema migrans are not completely clear. One explanation is presumably clinicians' desire to prevent the subjective symptoms that 10% to 20% of patients in most treatment trials experience after completion of therapy (10, 12). This rate, however, approximates the prevalence of reported background symptoms seen in "healthy" populations (3, 17) and in control groups in long-term studies of Lyme disease (18). There is no evidence that such symptoms represent active infection. In a recent study, *B. burgdorferi* could not be detected by culture or polymerase chain reaction in 129 persons with subjective symptoms after treatment for Lyme disease (19). In double-blind, randomized, placebo-controlled treatment trials in such persons, no benefit was observed for those who received an intensive antimicrobial treatment regimen consisting of intravenous ceftriaxone for 1 month followed by oral doxycycline for 2 months (19). In future prospective treatment studies of Lyme disease, inclusion of an appropriate control group of uninfected persons at the outset would be helpful in distinguishing the true incidence of "post-Lyme syndrome" from background symptoms (20).

Because U.S. patients with Lyme disease present sooner than they did in the past, erythema migrans is usually characterized by a homogeneous rash rather than by a target appearance or central clearing. There is no evidence that treatment with more than 2 weeks of antibiotics improves the prognosis, which in any case is excellent. Objective review of the information from clinical studies should change the way we think about diagnosing and treating early Lyme disease.

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"Did This Drug Cause My Patient's Hepatitis?" and Related Questions

What should the busy internist do when his or her patient, while taking several medications, suddenly develops a new clinical problem, such as hepatitis? Is the acute hepatitis drug related? If so, which drug is to blame?

The case report by May and colleagues in this issue (1) describes a 49-year-old electrician who developed acute scleral icterus and moderate biochemical hepatitis (total bilirubin level, 8.0 times the upper limit of normal; alanine aminotransferase [ALT] level, 6.8 times the upper limit of normal). The patient had been receiving several medications for years; he began taking pioglitazone, first at a low dosage (15 to 30 mg/d) for 6 months and later at a higher dosage (45 mg/d), for 1 week. Because the authors suspected that pioglitazone was the causal agent, they discontinued use of that medication; they continued all the others. The result of a thorough evaluation for other common causes of hepatitis (including other medications) was negative, and a liver biopsy showed a pattern of mixed hepatocellular–cholestatic injury compatible with drug hepatotoxicity. Liver function tests showed considerable improvement 2 weeks after pioglitazone therapy was discontinued. The authors concluded that the hepatitis was probably caused by pioglitazone, even though only one other similar case had been reported previously.

PERTINENT QUESTIONS FOR THE PRACTICING INTERNIST

This case report is clear and straightforward, but it does raise some additional interesting questions for the reader.

How Should I Assess Whether a Specific Drug Caused a New Clinical Syndrome in My Patient?

Several algorithms have been developed to help clinicians deal with this question. A simple but useful approach involves addressing five specific questions (2). This approach can be illustrated by applying it to this case.

1. *Has this type of adverse reaction been observed previously?* The package insert for pioglitazone states that in clinical trials in the United States, 4 of 1525 participants who received active treatment (0.26%) and 2 of 793 participants who received placebo (0.25%) achieved ALT levels greater than three times the upper limit of normal; these elevated ALT levels were reversible and were not clearly drug-related. Standard printed drug compendia, on-line drug databases, and published monographs (3–5) stated that no cases of pioglitazone-induced hepatitis had been reported. A MEDLINE search uncovered one published case report describing a patient who developed pioglitazone-induced hepatitis that was asymptomatic but severe enough (ALT level, 7.5 times the upper limit of normal) to require drug cessation (6).

2. *Was the timing appropriate?* Some drugs commonly produce their toxicity after a few minutes (for example, penicillin-induced anaphylaxis), while other drugs usually take months to produce a new condition (such as amiodarone-induced pulmonary fibrosis). The patient in this case report and the patient described previously each developed hepatitis after 6 to 7 months of therapy. Perhaps this timing represents a typical duration of drug exposure before the development of pioglitazone-induced hepatitis, and indeed, this delay would be consistent with that of troglitazone-induced hepatitis; however, we cannot generalize on the basis of only two reports.

3. *Does the problem improve with discontinuation of therapy with the drug?* Yes, in both cases, with dramatic improvement noted after just a few weeks.

4. *Does the problem recur with re-exposure to the potential culprit?* This was not attempted in either patient.

5. *Were other likely causes of hepatitis excluded?* In both case reports, extensive workups ruled out other common causes of hepatitis.

Thus, close analysis of this case report suggests that pioglitazone probably caused the symptomatic hepatitis, although a definitive conclusion is unattainable without additional prior cases reports and without a positive drug rechallenge. The approach outlined here becomes more problematic when the drug is relatively new and clinical experience with it has been limited. This concern leads us to focus on a second important question.

When a New Drug with Limited Clinical Experience Appears To Have Caused an Acute Drug Reaction, Can I Refer to Cases Involving Earlier Drugs in the Same Class?

Can the more extensive experience documented for two earlier drugs from the thiazolidinedione class—

troglitazone and rosiglitazone—help us? Is the potential toxic effect observed in this patient a class effect or one that is specific to just one drug in the class? We know more about the earlier drugs from this class, but similar drugs in a class may differ substantially in toxicity profile. Cerivastatin, for example, apparently is much more likely to cause fatal rhabdomyolysis than are other statin drugs (31 cases have been spontaneously reported); thus, cerivastatin was removed from sale in the United States in August 2001. Because methicillin appeared much more nephrotoxic than its classmates nafcillin and oxacillin, it is no longer used in the United States as an antistaphylococcal antibiotic. Considering the reservations about class effects, what can we learn?

We find that troglitazone was the first drug from the thiazolidinedione class approved by the Food and Drug Administration (FDA) for sale in the United States in January 1997. During the preapproval phase of clinical drug testing, 1.9% of treated patients had ALT levels greater than three times the upper limit of normal, compared with 0.6% of patients receiving placebo (a relative risk of about 3); neither the manufacturer nor the FDA was aware of more serious hepatotoxic reactions. After the FDA approved the drug, more cases of hepatitis of varying severity (but including fulminant liver failure, sometimes requiring transplantation or leading to death) were spontaneously reported in the United States and in other countries. Because of these reports, the drug was withdrawn from the market in the United Kingdom in late 1997. In March 1999, an FDA advisory committee noted that 43 cases of acute hepatic failure (with 29 deaths) among 1.2 million patients who had received the drug had been spontaneously reported (approximately 0.004% of patients receiving the drug). When the drug was finally removed from the U.S. market in March 2000, 61 cases of acute hepatic failure had been reported (3). The mechanism of troglitazone-induced liver damage is still unclear (7). Liver biopsy or autopsy findings showed various patterns of liver damage (most often hepatocellular damage or mixed hepatocellular–cholestatic injury), and liver toxicity most commonly developed after months of drug use (7–16).

This brief history of troglitazone's availability in the United States illustrates several important points. First, warnings as part of the required drug labeling may be inadequate to protect patients. (The FDA required the official labeling of the drug to be changed at least five times before its removal from the market, including progressively more serious warnings about the drug's ability to cause hepatotoxicity.) Second, premarketing clinical testing (which, for many drugs, involves 1000 to 3000 human participants) cannot adequately delineate the full range of possible acute drug reactions or the actual frequency of rare reactions. Finally, while the problem of mild hepatitis was noted fairly early (occurring in perhaps 1.9% of patients), the problem of life-threatening fulminant hepatic failure took much longer to recognize, partly because it occurred much less frequently (in perhaps 0.004% of exposed patients).

The problem of drug-induced hepatotoxicity appears less severe with rosiglitazone, which was the second drug of this class to be approved by the FDA (in May 1999). Clinical studies of 4598 patients treated with rosiglitazone revealed no evidence of drug-induced hepatotoxicity or elevated ALT levels. In additional clinical trials, approximately 0.2% of patients treated with the active drug and approximately 0.2% of the patients receiving placebo developed elevated ALT levels more than three times higher than the upper limit of normal, for a relative risk of mild hepatitis of approximately 1 (17). Despite this impressive early record of safety in clinical trials, two case reports have recently described patients who received rosiglitazone for several weeks and developed reversible but severe hepatocellular injury (17) or hepatic failure (18). The frequency of such rare but severe reactions is unknown.

Eli Lilly and Co. (Indianapolis, Indiana) and Takeda Pharmaceuticals North American (Lincolnshire, Illinois), which have jointly marketed pioglitazone (as Actos) in the United States since its approval in July 1999, make various detailed recommendations concerning potential hepatotoxicity in the precautions section of the package insert. They mention the potential class effects of thiazolidinedione-induced liver toxicity and the need for ongoing postmarketing studies. They recommend performing baseline liver function tests before the drug is started, proceeding with caution if the baseline ALT level is mildly elevated, and avoiding the drug if the baseline ALT level is greater than 2.5 times the upper limit of normal. They further recommend monitoring liver function test results every 2 months during the first year of drug therapy and discontinuing use of the drug if the ALT level increases to greater than three times the upper limit of normal or if clinical hepatitis develops.

Because rare but serious acute drug reactions are often discovered only after a drug has been approved for use by the FDA, prescribers have a special obligation to help the FDA identify severe cases that have been recognized after FDA approval is granted. This leads us to a third important question.

What Are My Obligations as a Practicing Physician To Report Suspected Acute Drug Reactions to the Drug Manufacturer or the FDA?

The thoughtful physician has a professional obligation to report new, unexpected, or serious acute drug reactions to the manufacturer, the FDA, or both. Most physicians find it easiest to file such reports directly with the FDA via the convenient MedWatch program. The form for reporting, which is available at www.fda.gov/medwatch/safety.htm, is just two pages long and takes only approximately 10 minutes to complete. The FDA specifically wants to be notified when the suspected acute drug reaction is serious—that is, if it results in death, causes a life-threatening condition, necessitates or prolongs hospitalization, causes permanent disability or congenital anomaly, or requires intervention to prevent serious impairment. The FDA asks all health care providers to report suspected serious reactions even if available information is incomplete or if the provider cannot clearly identify the drug as the cause.

CONCLUSIONS

So, where do these questions and their answers leave the busy but thoughtful internist? It now appears highly probable (but not definite) that pioglitazone can cause symptomatic, mild-to-moderate drug-induced hepatitis, as reported by May and colleagues (1). We are uncertain about the actual frequency of this reaction and about why some patients develop the reaction while others do not; however, such acute drug reactions almost certainly occur much less commonly among pioglitazone users than among troglitazone users. (Compared with placebo use, the relative risk is approximately 1.0 for pioglitazone users and approximately 3.0 for troglitazone users.) Rosiglitazone has been shown to cause serious liver damage or liver failure, but such severe acute drug reactions appear to be rare. As we gain more experience with pioglitazone, we may learn that it too may cause such severe hepatotoxic reactions. If pioglitazone is confirmed to have this rare side effect, an approximate frequency will not be known until the drug has been given to large numbers of patients for several years, assuming that prescribers file the appropriate spontaneous reports with the FDA.

Internists will encounter numerous episodes of possible acute drug reactions in their clinical practice every month and will need to become comfortable with a simple plan for evaluating such cases of potential drug-induced disease. The approach outlined here should help identify "guilty" drugs whose use should be discontinued and "innocent" drugs whose use should be "cleared" and continued. Finally, internists should remember to notify the FDA promptly—especially in cases involving a drug that is new to the market—when they believe they have observed a possible or probable acute drug reaction that meets a reasonable threshold of severity.

We should thank May and colleagues for bringing this probable acute drug reaction to our attention and (via MedWatch) to the attention of the FDA and for indirectly raising these additional important clinical pharmacology issues. The most important question is, What will *Annals* readers do with the next possible acute drug reaction that they discover in their own clinical practice?

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On Growing Old

What happened to that skinny kid—the one so skinny her ribs could be counted just by looking? Today, she is a twittery, purse-clutching, cane-wielding, pill-popping little old lady living alone. Still skinny, she prefers the term *petite*. It sounds better.

I am that skinny kid. I'm missing a few parts and have replaced several of the worn-out ones. Then, there are all the abuses suffered by this 88-year-old body. Nothing prepares you for old age. You get out of bed one morning and *voila*! A bolt out of the blue and you can no longer function normally. What to do? Now, there is ample time not only to smell the roses but also to discuss my aches and pains with others of my ilk.

What an impressive array of pills I have. Group one is simple—just one pill to take when I get out of bed. For a half hour after group one, no eating, drinking, or lying down. The group two pills must be taken on an empty stomach. Then, I can have breakfast and take group three pills. Group four are doled out into a little dish, and I take them on a catch-as-catch-can basis, meaning when I remember. I keep the group four pills in the cupboard; otherwise, they clutter the counter. As soon as I have a workable system, my doctor changes everything. From four pills to two and a half, for example. I do not have much luck splitting a tiny pill, so I guess I am healthier on some days than on others. Whatever.

About the missing parts: The clerk at the shoe store did a double take when he removed my right shoe and saw that a big toe was missing. He shook my shoe and when nothing emerged, he peered into it. Emptiness.

The first sight of the disfigurement caused by my breast removal prompted me to tell the doctor he needed sewing lessons. He had left me lumpy and bumpy. Today, I have a hard time telling whether anything had ever been there. Hardly a scar shows. Although I think a Band-Aid would have sufficed, I went to the store to see about a prosthesis. I was shown what looked like a bird cage made of iron. If I put it on, I would have fallen on my face. My daughter-in-law gave me some small shoulder pads removed from a garment. Just the thing to even me out.

My right total hip replacement is working out just fine. My dentures fit most of the time. I need a cataract operation for the left eye. I bought hearing aids so I could enjoy a sermon, a play, a movie, or just nice conversation. I wish. I plainly hear the rustling of the day's calendar, sneezing, coughing, and babies fussing. On occasion, I hear a word here and there, but the minister's jokes go by me like a bat out of a cave. Coffee time after the service is bedlam—the Tower of Babel. The aids reposing on the mantel do nothing to enhance the decor of the room, but I do use them to watch television when I am alone, when I remember. More often, I forget, and the volume is such that I do not hear the phone or the doorbell. Hard as I try, I cannot adjust them to my liking. I have met only one person who has admitted to being satisfied, but then, I have not met everybody. My condition seems to have worsened, so maybe I should learn sign language. But with whom could I converse? I doubt lipreading would be the ticket for me. Have you watched people speak? In my opinion, no two pair of lips form a word in quite the same way. Simply put, I would be at sea.

Everyone is quick to tell me that my pacemaker protrudes because of lack of flesh. Had I known this in advance, I would at least have asked that the pacemaker be installed a few inches lower, under a fleshier part of me. I check it at home every 3 months by phone and once a year at the hospital. So far, all is well, although it did show that I had a heart attack somewhere down the line. I have not the faintest idea when or where—nor does the doctor. I think they are called *silent ones*.

Ulcers? How many bottles of Mylanta and other medications have I taken without relief? One test turned out rather worrisome for a particular individual—me! Rubber tubing, about the width of a pencil, was to be inserted into my stomach, withdrawn, and reinserted for a certain number of times. All went well the first time. The next time, 14 inches of the tube broke off and remained in my stomach. I was closely monitored. I even posed for a picture during the week or more that the tubing remained in my stomach. I clearly saw it stretched out full length in my intestines—an interesting sight. Another test took some jostling to get me into position before the nonflexible tubing was inserted into my stomach. My delight at the successful completion of the task dwindled when I heard the words: "the light

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isn't working, Mrs. Lundberg." The arrival of Tagamet on the market did the trick for my ulcer.

I am inclined to believe my Graves disease is the most dismaying. Although I fell down a couple of times without injury or pain, I felt robbed of my self-confidence. I do not really need a cane, but I have come to depend on one, even though I just carry it.

I recall the 9 days I spent in the hospital for an operation on my football knee. That time was a vacation for me. I had no discomfort. I just had to keep from bending my knee. I was free to scoot around the halls in a wheelchair. I played cards with a young man who was badly injured in a car accident; I combed the gorgeous, curly, auburn hair of a young lady; and I generally kept myself busy.

My thyroid problem continues off and on. Once, I was isolated in a Chicago hospital and given radioactive iodine followed by pills. My feet began to swell, but the doctor assured me that it would be okay to go on an already planned 2-week trip. By the time my traveling companion and I got home, I could hear water gurgle in my heart. But I did have well filled-out legs—for once. Back into the hospital. By the time they let me go home, I weighed next to nothing. Years later, I had a similar episode in Duluth and was given one $500 pill. No muss, no fuss. I didn't even get into the doctor's office; received it standing in the doorway. My, modern science!

One of my more humorous (and true) events was when I received a mailing from, I think, the Mayo Clinic. The mailing contained an article on the seven signs of prostate problems. Oddly enough, shortly after ascertaining that I had every one of the symptoms, I had yet another medical problem and found myself in the emergency room. Of course, I asked the hospital staff to please check my prostate gland. The doctor in charge said, without a smile, that if I had that problem it would be one for the books. The next morning, the head nurse mentioned to me that she heard I had prostate problems.

The month spent at the nursing home after hip surgery was fun, except for the iron pills. I will have to be paid to take those pills ever again. I was fortunate to share a room with an old acquaintance. She did not speak very clearly, and I do not hear all that well, but we managed to enjoy ourselves and each other. We targeted the male nurses. Imagine my consternation when one came into the room and announced that he was taking me for a shower. I am innately shy, but I think I carried that one off rather well.

I've had arthritis for ages and ages. I began to get pain in my lower back and beyond, but the doctor did not put a name to it and just suggested Advil, so I called it arthritis. Some days, it took a good hour or more of activity to be able to move around comfortably. Quite suddenly, the pain decided to leave the lower part of me and settle in my upper half. After several bloodlettings and other testing, the doctor finally came to the conclusion I had polymyalgia rheumatica. I was impressed, but the best part was yet to come. The doctor prescribed prednisone, and believe it or not, two pills left me pain-free. Although I will gradually be taken off the pills, I remain pain free. I feel like a new woman—well, an old woman with some new parts!

Could it be that most families have an accident-prone child? If so, the numerous small scars from head to toe must mean that I am that child in our family. I acquired some when I was well into adulthood. I have had just one fracture, in a wrist. Then there are the cramps you have when you must get out of a warm bed and walk around until your big toes (toe, in my case) become normal instead of being locked in an upright position. Their shape always reminds me of the soft shoes worn by elves. And through the pain, I still manage a weak smile (or is it a sickly grin) when I hear, "Oh Grammahh!" from the grandchildren when they see the shape of my knuckle-locked hands. Grotesque, but fortunately, the condition is temporary—as is every condition, I have learned.

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ON BEING A DOCTOR

An Examination of Conscience

In the recent past, I had two febrile illnesses. The first was pneumonia. The second, despite immunization, was influenza.

During each of these illnesses, I had high fevers, shaking chills, and toxic delirium. And during the lucid moments of my first illness, my mind always seemed to return to my file of patients. Faces flew by. In sharpest focus were those who had died: effervescent, humorous Jean who made us laugh even as she was failing with chronic leukemia; gracious, courtly Franklin, who enthralled me with stories of his life and whose advancing infirmity prompted me to make housecalls, the memory of which now seemed most precious to me. I was overwhelmed with admiration for these brave patients. How many of them had presented an optimistic, often smiling persona during our short time together in the office or hospital, only subsequently to endure fear and uncertainty during long, lonely nights! In my feverish discomfort, I wondered how they had summoned the inner strength to deal with greater suffering and far more serious illnesses than my limited one. In fact, I became so overwhelmed by this feeling that during the fevers I asked my wife to write down my ramblings. It was a surprise to me when I read her notes after my recovery. She had captured the feelings I had experienced, yet they seemed other-worldly, as though the insights already were beginning to fade.

In more than 30 years of practice, I have cared for patients with serious hematologic disorders. My patients often require toxic chemotherapy, and many have a far-from-certain outcome. My own petty fevers made me wonder at these patients, that they could deal with the terrifying uncertainty that is often at the heart of their illness. I wondered, too, whether I had done enough to ease their discomfort and help them maintain hope. Even with this fever-induced "examination of conscience," when I recalled that many patients and family members of deceased patients had told me that our relationship had helped them cope with the struggle, I wondered if it had been enough.

My second fever, some 8 months later, reinforced these notions, but gave me another, deeper insight as well.

On the day my second illness struck, I was scheduled to speak at medical grand rounds. Despite chills, fever, and aching, I gave the talk. Feeling like the battle-scarred soldier, I was anxious to leave for home and return to my sickbed and to my wife's constant attention. My secretary detained me, knowing I would want to take a call about Shirley. Her husband, John, was on the telephone.

Shirley had become my patient many years before, soon after I joined the medical school faculty. She was 32 years old then and had presented with autoimmune hemolytic anemia. At age 17, she had had a thymectomy that revealed Hodgkin disease. We found that the Hodgkin disease had recurred. We treated her with total nodal radiation, which undoubtedly led to many of her subsequent medical problems, including premature coronary artery disease, breast cancer, and esophageal strictures. But the Hodgkin disease never recurred.

Despite her many complications (and febrile illness far more worrisome than mine), Shirley's chief concern in life remained her mildly retarded daughter, whose erratic behavior caused continual heartache for John and Shirley.

Over the 31 years that I followed Shirley, a visit would consist first of a quick discussion of symptoms and a physical exam. But for most of the visit, we would talk about her life, her daughter, and her husband. I would relate a humorous event, hold her hand, and hug her. She told John and me that she could always smile during our visits and that she felt more hopeful afterward, even when things were not going well. Did she mean it, I wondered now with my newfound insights, or was this simple courtesy?

After a year of seriously declining health, Shirley had just been admitted to intensive care for worsening pulmonary status and increasing debility. The pulmonologist was to meet with John and Shirley to discuss performing bronchoscopy and transbronchial biopsy. I explained that with my active influenza I could not come to see Shirley or talk with the two of them in person. John and I discussed her continuing decline in health and increasing discomfort over the last 6 months despite aggressive therapy and her best efforts. We discussed the proposed procedure and her prognosis, including the unlikely possibility of finding a reversible

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process. We agreed that Shirley's wishes should determine further management. Since she was, at that time, in and out of awareness, John would be guided by his years of devoted involvement with her, and also by my knowledge of choices that Shirley had made in past years when faced with critical medical decisions. Following our conversation, John talked with the intensive care unit team. I was not surprised to learn later that all agreed only comfort care should be provided. Shirley died within 24 hours.

On that day I realized what the personal connection to Shirley had meant to me as her physician, how much it had meant to be her doctor, and how much my sense of myself as a good doctor had depended on the connection forged between my patients and me. I needed, I confess, to hear more. I was not yet ready for her leaving me. With this profound loss came the shared sense of deprivation patients must endure repeatedly because of illness. My own illness had deprived me of seeing my longtime patient and friend in her final hours. I could neither comfort her, nor hold her hand, nor say goodbye. This emptiness for me was overwhelming. I wondered whether Shirley had needed to see me as much as I had her.

Petty illness, trifling fever, transient myalgias had led me to something more: a desperate need to hold onto that something that is the very essence of doctoring.

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Diagnosing Primary HIV Infection

TO THE EDITOR: Daar and colleagues' (1) primary conclusion—that symptoms do not allow focused screening for primary HIV infection—may not be justified since "compatible symptoms" in part determined inclusion in their study and performance of their gold standard test. Furthermore, the statement that clinicians may be confident that "more than 90%" of patients with primary HIV infection will be identified by a standard HIV p24 antigen test alone is potentially misleading for several reasons. First, the study's sensitivity estimate of 88.7% for the p24 antigen test is relatively imprecise, with a 95% CI whose lower boundary was 77%. Second, the sensitivity of the p24 antigen assay depends on the time between onset of symptoms of primary HIV infection and screening, since antigenemia disappears during primary HIV infection (2). Significant delay before diagnosis of primary HIV infection may be typical in areas other than those served by well-connected clinics in urban centers.

The **Figure** illustrates our experience screening potential patients from the rural southeastern United States for a primary HIV infection treatment trial. Only 8 of 21 patients with confirmed primary HIV infection (38%) had positive results on p24 antigen assay. Primary HIV infection was defined as positivity for HIV RNA or DNA and negative results on enzyme-linked immunosorbent assay or an evolving Western blot within 30 days. The median time from onset of symptoms to screening in our cohort was 26 days (range, 5 to 70 days); this interval was greater than 21 days for most p24-negative persons (11 of 13). Since most of the published literature on treatment of primary HIV infection (3) includes patients with evolving Western blot who had onset of symptoms several weeks previously, these 11 patients should be considered to have true primary HIV infection. Last, the cost-effectiveness of an approach using p24 antigen testing cannot be adequately addressed by the data provided by Daar and colleagues. Formal cost-effectiveness studies, which consider, for instance, the potential adverse impact of false-negative results on sexual transmission rates (4) and therefore public health, are warranted.

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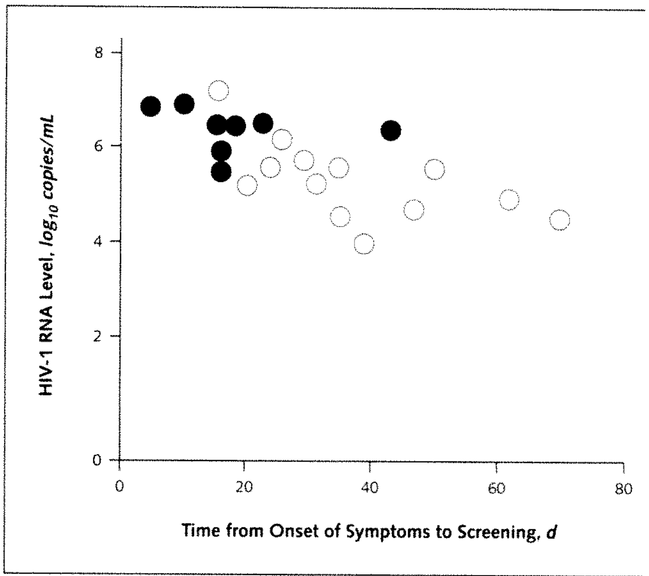
Figure. **Measurements of HIV-1 RNA plasma viral load in 21 patients with confirmed primary HIV infection who had positive (*black circles*) or negative (*white circles*) results on p24 antigen assay.**



The Roche Amplicor Ultradirect Assay (Roche Diagnostics, Branchburg, New Jersey) was used to measure HIV-1 RNA in blood plasma (lower limit, 50 copies/mL); p24 antigenemia was measured in stored serum specimens (HIVAG-1 Monoclonal, Abbott Laboratories, Abbott Park, Illinois).

IN RESPONSE: Our study was designed to distinguish between symptomatic patients who had primary HIV infection and those who did not. Since primary HIV infection can present with a broad range of clinical manifestations (1), all referred patients, regardless of symptom complex, were screened. Thus, on the basis of our analysis, which is consistent with that of others (2), we stand by our conclusions that screening should not be limited to patients with select symptoms.

We agree that our estimate of p24 antigen sensitivity could be misinterpreted. Nevertheless, our study demonstrates that this assay can be used to diagnose primary HIV infection in symptomatic, seronegative persons. Clinicians should be aware that sensitivity decreases over time and may vary according to the assay used. As noted in our article, regardless of the virologic test used, all at-risk persons should be counseled about the need for follow-up testing.

Pilcher and colleagues take issue with our focus on patients who were negative for HIV antibody, arguing that studies of primary

HIV infection often include the weeks or months from seroconversion. The objective of our study was to define the utility of virologic tests in diagnosing primary HIV infection during the seronegative window. After all, this is the setting in which the diagnosis is missed if virologic testing is not performed (3, 4). Moreover, patients with positive results on enzyme immunosorbent assay do not need a virologic test to establish their HIV status. Thus, we clearly state in our article the importance of assessing the sensitivity of virologic tests in the context of the clinical setting and the serologic status of the patient. The absence of serologic results in the data provided by Pilcher and colleagues only strengthens this point. Their Figure suggests that they have screened very few patients within the first weeks of infection, when a virologic test is likely to be necessary. Furthermore, the few patients that they have tested during the first weeks appear to be positive on p24 antigen assay, consistent with our observations.

We agree that a formal analysis of cost-effectiveness needs to incorporate the impact of false-negative results. However, such an analysis must also include the significant adverse psychological and financial effects of false-positive results. By defining the characteristics of each assay, our study allows clinicians to make informed decisions about the optimal screening strategy for specific patients in select clinical settings.

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Regression and Progression of Valvulopathy Associated with Fenfluramine and Phentermine

TO THE EDITOR: We read the reports by Mast and colleagues (1) and Weissman and coworkers (2) with interest. Because the combination of fenfluramine and phentermine ("fen-phen") was used extensively in our area, we have asked all patients presenting at our institution for echocardiography in the past 3.5 years about use of these drugs. Data from our registry have been reported elsewhere (3).

One hundred twenty patients in our registry had follow-up echocardiography at least twice after cessation of fenfluramine–phentermine use. The mean age of these patients was 49 years, and the mean duration between echocardiograms was 10.6 months. Ninety-nine patients met U.S. Food and Drug Administration (FDA) criteria for valvulopathy (mild or greater aortic insufficiency or moderate or greater mitral regurgitation) on first echocardiography. On second echocardiography, 57 of these 99 patients showed no change in valvulopathy (57.6% [95% CI, 47.8% to 67.3%]), 33 showed improvement in valvulopathy (33.3% [CI, 24.1% to 42.6%]), and 9 showed deterioration in valvulopathy (9.1% [CI, 3.4% to 14.8%]). Nine patients no longer met FDA criteria for valvulopathy. Of the 21 patients without valvulopathy on first echocardiography, none met FDA criteria for valvulopathy on second echocardiography.

At our institution, the condition of most patients who developed valvulopathy after use of fenfluramine–phentermine remained unchanged after approximately 1 year. Valvulopathy improved in a substantial number of patients but worsened in a small but still significant number. We can be hopeful that some of our patients will eventually improve, and we are certainly encouraged that no patients developed new valvulopathy. However, because approximately two thirds of the patients in our registry have not improved, we believe that physicians must continue to be vigilant with patients who developed valvulopathy after fenfluramine–phentermine use.

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Appropriate Use of Antibiotics: Pharyngitis

TO THE EDITOR: In March 2001, Snow and colleagues (1) and Cooper and associates (2) proposed a practice guideline for management of acute pharyngitis in adults. This guideline is a major departure from the current recommendations of expert panels of the Infectious Diseases Society of America (3), the American Heart Association (4), and the American Academy of Pediatrics (5) regarding diagnosis of pharyngitis caused by group A streptococci. We believe that certain aspects of the proposed practice guideline, such as eschewing the throat culture as a standard of diagnosis for acute streptococcal pharyngitis in adults, are debatable. Even more troubling is the endorsement of the use of clinical criteria alone, without even confirmation by a rapid antigen test, for management of acute pharyngitis. The guideline recommends that the four-factor algorithm proposed by Centor and coworkers (6) be used when deciding whether to treat with antibiotics. This algorithm can be useful in clinical decision making, particularly in identifying patients whose risk for streptococcal infection is too low to justify microbiological tests. Centor and coworkers did not, however, propose that the algorithm replace such tests.

Although Snow and Cooper and their colleagues allow options for using rapid antigen tests, it is extremely unlikely that clinicians will elect to perform such tests when a guideline endorsed by the American College of Physicians–American Society of Internal Medicine allows decision making on clinical grounds alone. The authors state that a major goal of their guideline is "dramatically decreasing excess antibiotic use" (1). Will their proposal to avoid diagnostic tests and limit antibiotic therapy to patients with three or four Centor criteria actually accomplish this objective?

In the Centor study, only 10% of "adult" patients (patients >15 years of age) presenting to an urban emergency department with pharyngitis had all four predictive factors; in this group, the probability of a positive throat culture for group A streptococci was 56%. In the 20% of patients who had three factors, the probability of a positive culture was only between 30% and 34%. According to these data, if the proposed guideline's strategy of clinical management alone were followed, 60% of patients for whom antibiotics were prescribed would have had negative results on microbiological tests (throat culture or rapid antigen test).

We must conclude, therefore, that the proposed algorithm-based strategy would result in antimicrobial treatment of an unacceptably large number of adults with nonstreptococcal pharyngitis. This is particularly unfortunate in an age group with low prevalence of streptococcal pharyngitis and exceedingly low current risk (in developed countries) for acute rheumatic fever. It should be noted that the Infectious Diseases Society of America did not endorse the proposed clinical practice guideline. The authors themselves suggest that "prospective studies should be conducted to compare these strategies in terms of relevant patient outcomes and cost" (2). Should not such studies be completed before established methods of diagnosis and treatment of streptococcal pharyngitis in adults are abandoned?

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Sleep Apnea and Gastroesophageal Reflux Disease

TO THE EDITOR: Obstructive sleep apnea is a common condition and is associated with increased risk for hypertension, myocardial infarction, stroke, cardiac arrhythmia, headache, and traffic and industrial accidents (1). The condition may be simple to recognize. An overweight, middle-aged man who presents with a chief complaint of falling asleep during the day, who snores loudly, and who has been observed by his bed partner to stop breathing in his sleep poses no diagnostic challenge. A patient may, however, present with a complication of obstructive sleep apnea; in this case, suspicion of sleep apnea may lead to effective therapy. We report the case of a physician whose severe symptoms of gastroesophageal reflux disease (GERD) were substantially relieved by treatment of his sleep apnea.

A 65-year-old physician had been treated for 8 years for severe GERD. He would awaken every night choking and coughing from reflux of acidic gastric fluid. Omeprazole was beneficial, but the patient was concerned about taking this drug for long periods. He took approximately 15 calcium carbonate tablets per day for symptom relief. An interest in sleep medicine and a concern about his snoring and his tendency to fall asleep at the theater led him to have polysomnography. The test showed severe sleep apnea, with a supine respiratory disturbance index of 80 per hour and oxygen desaturation during sleep to 88%. Nasal continuous positive airway pressure, at a pressure of 10 cm of H_2O, eliminated all apneas. Within a day of beginning this therapy, nocturnal awakenings due to reflux stopped completely and have not returned in 2 years of follow-up. Daytime symptoms of GERD were markedly improved, and consumption of calcium carbonate tablets decreased from approximately 15 per day to 3 per day.

Gastroesophageal reflux disease is a common illness that not only causes pain and discomfort but also has important complications, including asthma, Barrett esophagus, and esophageal cancer (2). Symptoms of GERD are common during sleep. Regurgitation of acidic gastric fluid may cause discomfort, choking, aspiration, and disturbed sleep with multiple awakenings. A major text of sleep disorders (3) states that esophageal reflux is a frequently observed symptom among patients with obstructive sleep apnea. Continuous positive airway pressure is the most effective therapy for obstructive sleep apnea and may reduce the severity of gastrointestinal reflux in patients with both conditions. We urge physicians to inquire about symptoms of sleep apnea in patients with GERD.

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A Rollover Epidemic in North Dakota from 1994 to 1997

TO THE EDITOR: During the past few years, I felt that reports of vehicle rollovers in the news media were increasing. Also, in 1996, a patient who replaced roofs of sport utility vehicles (SUVs) told me something that stuck in my mind: He could never find enough accident-damaged SUVs with intact roofs to repair SUVs that had only roof damage. Since I have a teenager who is of driving age, I decided to study the issue.

I obtained copies of *North Dakota Vehicular Crash Facts* for 1994 through 1997 (1–4). These publications detailed all aspects of fatal and nonfatal vehicle crashes during these years, including but not limited to alcohol or drug use, speeding, seat belt use, type of driver violation, road surface, weather conditions, type of roadway (urban vs. rural), age and sex of the driver, and speed limits. I carefully analyzed the exact nature of the first harmful event in all crashes, as abstracted from standardized crash reports (Table).

Table. **North Dakota Crash Statistics**

Variable	Rates per 100 Million Vehicle Miles Traveled			
	1994	1995	1996	1997
Total crashes	219.670	215.370	235.950	242.00
Rollover crashes	16.900	20.550	24.550	30.950
All crash injuries	88.660	86.650	88.910	85.690
Rollover injuries	7.280	8.177	10.080	11.460
All crash deaths	1.378	1.116	1.256	1.525
Rollover deaths	0.2970	0.3319	0.4138	0.4790

On the basis of my analysis, I concluded that our vehicles are suffering from "rolloveritis." Nearly 5000 rollover crashes, 2500 rollover injuries, and more than 100 rollover deaths occurred in North Dakota alone from 1994 to 1997. These numbers are probably related to a basic change in what we are driving. Pickups and SUVs, which have high centers of gravity and have become more popular for highway driving during the past decade, are the likely culprits in this epidemic. Buyer beware!

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BOOK NOTES

Structured abstracts of information on newly published books, computer programs, selected Web sites, and other material are provided in this portion of Medical Writings. "Order phone" numbers can be used to place orders directly with publishers.

Practical Neuro-Oncology: A Guide to Patient Care

McAllister LD, Ward JH, Schulman SF, DeAngelis LM. 316 pages. Boston: Butterworth-Heinemann, 2001. $39.99. ISBN 0750671807. Order phone 800-366-2665.

Field of medicine: Neurology and oncology.

Format: Softcover book.

Audience: General neurologists, primary care physicians, radiation oncologists, medical oncologists, neurosurgeons, and nursing or hospice personnel.

Purpose: To provide a concise handbook of basic diagnosis and treatment of primary and metastatic central nervous system tumors and common clinical problems encountered by all physicians caring for patients with these tumors.

Content: The first part summarizes the types of primary brain tumors of the central nervous system, including genetic syndromes and risk factors. The next section discusses clinical presentations of brain and spinal cord tumors, diagnostic imaging of brain, cerebrospinal fluid analysis, and pathologic diagnosis. The following sections cover common astrocytic neoplasms, pituitary tumors, meningiomas, primary central nervous system lymphoma, and brain and spinal metastases. The second half of the book discusses common clinical problems encountered in neuro-oncology, including seizures, infections, deep venous thrombosis, depression, and urinary problems.

Highlights: There are excellent tables on hereditary syndromes associated with brain tumors, antiepileptic drugs, and pain medications. The chapters on lumbar puncture interpretation, corticosteroid use, pain management, and terminal care are well presented. A chapter on clinical trials helps primary physicians facilitate participation of their patients in investigational studies, and an appendix contains a valuable list of information and services available to patients with brain tumors, including Web sites and hospice organizations.

Limitations: The physical diagnosis chapters recapitulate standard localization and diagnostic principles found in many standard textbooks, although it is helpful to have this information accessible in one volume. The pathologic diagnosis section is only two pages long and, like many chapters, refers the readers to references that are large textbooks rather than specific articles. Since many clinical "pearls" are covered in tables or outlines, there is no room for detailed discussion of controversial issues, such as the risk for brain tumors from cellular telephones.

Related reading: Several larger textbooks, such as Bigner and colleagues' *Russell and Rubinstein's Pathology of Tumors of the Nervous System*, 6th edition (Oxford Univ Pr, 1998), cover brain tumor pathology, and general medical problems are covered in textbooks such as Murphy and colleagues' *American Cancer Society Textbook of Clinical Oncology* (American Cancer Society, 1995). Primary brain tumors are covered in more detail in Schold and colleagues' *Primary Tumors of the Brain and Spinal Cord* (Butterworth-Heinemann, 1997) and Bernstein and Berger's *Neuro-Oncology: The Essentials* (Thieme, 2002).

Reviewer: Amy A. Pruitt, MD, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania.

Field Guide to Urgent and Ambulatory Care Procedures

James DM. 351 pages. Philadelphia: Lippincott Williams & Wilkins; 2001. $29.95. ISBN 0781728231. Order phone 800-638-0672.

Field of medicine: Ambulatory general medical care.

Format: Softcover book (pocket-size).

Audience: Primary care (general internal medicine, family medicine, and pediatrics) and sports medicine physicians working in an outpatient, ambulatory, or urgent care setting.

Purpose: To provide a straightforward, rapid, and simple guide to common procedures used in a general outpatient setting.

Content: The handbook is divided into 70 chapters through 11 organ systems and a section on advanced procedures. Thirty of these chapters deal with traumatic events; the largest section focuses on musculoskeletal procedures (encompassing 18 chapters and 74 pages).

Highlights: Very well organized; each chapter has an introductory section, materials required, clinical technique, and practical tips section. Excellent diagrams accompany text in nearly all chapters. Newer techniques (such as automated external defribillation units and octylcyanoacrylate) are well covered. The author has met his goal of demystifying medical procedures and outlining them in a clear, straightforward matter.

Limitations: Focus is primarily on adults; infants and children are not completely addressed. Shoulder dislocation section should also visually demonstrate the traction–countertraction technique (Respet PB. A practical technique for reducing shoulder dislocations. *Journal of Musculoskeletal Medicine.* 1988;5:29) in addition to the Stimson technique. An appendix with suggested equipment required for a clinic setting would be useful. The sections on peritoneal lavage and arthocentesis should include criteria for interpretation of aspirate fluid results. A chapter on management of long-term indwelling catheters, shunts, and fistulas would be useful, as would trigger-point therapy for myofascial pain treatment.

Related reading: Rosen and colleagues' *Atlas of Emergency Procedures* (Mosby, 2001) is a concise guide focusing on the emergency department setting and complements their multivolume comprehensive textbook of emergency medicine. Roberts and Hedges' *Clinical Procedures in Emergency Medicine*, 3rd edition (WB Saunders, 1998), is the standard comprehensive hardcover reference in the field.

Reviewer: Jerrold B. Leikin, MD, Evanston Northwestern Healthcare OMEGA, Glenbrook Hospital, Glenview, Illinois.

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YOUR PATIENT:

A 45-year-old woman presents with weight loss of approximately 9 kg (20 lb) over the past 12 months. She has been aware of no change in appetite. She eats three meals daily and snacks most evenings. Her activity has similarly been unchanged. She exercises by walking 2 to 3 miles three or four times weekly. She takes no medication and reports no alcohol or drug use. Review of systems reveals a 1- to 1.5-year history of a pruritic rash on the trunk and extremities. She reports occasional vague abdominal pain and bloating, which subside spontaneously in a few hours, and notes the passage of flatus. She has no food intolerance, difficulty swallowing, sweating, tremor, constipation, diarrhea, or arthritis. She has normal, regular menstrual periods and has two to three stools per day, with no recent change.

The patient is 175 cm (69 in) tall and weighs 50 kg (110 lb). Blood pressure is 115/70 mm Hg, pulse is 96/min, and temperature is 36.9 °C (98.4 °F). The skin shows a truncal and proximal extremity rash consisting of grouped vesicles on an erythematous base. There is also evidence of excoriation. The remainder of the physical examination, including pelvic and rectal examination, is otherwise normal, and stool is negative for occult blood. The neurologic examination is normal.

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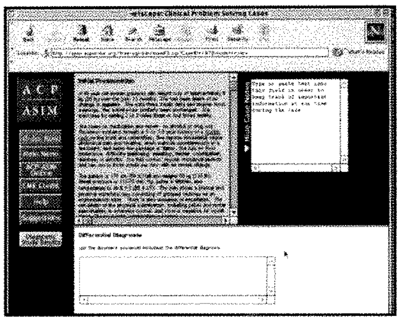

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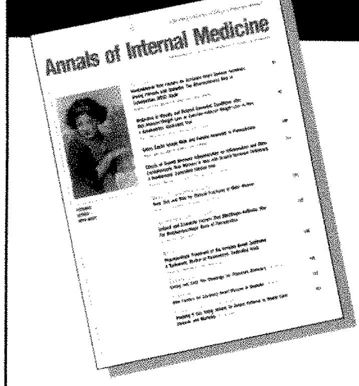

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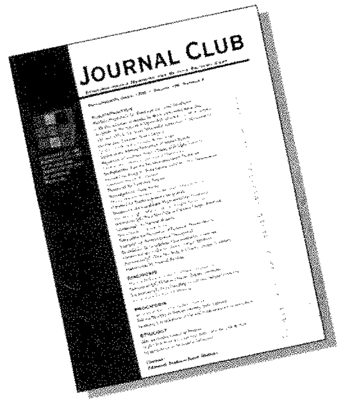

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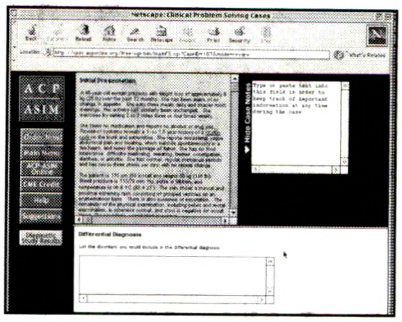

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ARTICLES

Effect of Aerobic Exercise on Blood Pressure: A Meta-Analysis of Randomized, Controlled Trials 493

S.P. Whelton, A. Chin, X. Xin, and J. He

Exercise reduces blood pressure in both hypertensive and normotensive persons. An increase in aerobic physical activity should be considered an important component of lifestyle modification for prevention and treatment of high blood pressure.

Administration of Neutral Protamine Hagedorn Insulin at Bedtime versus with Dinner in Type 1 Diabetes Mellitus To Avoid Nocturnal Hypoglycemia and Improve Control. A Randomized, Controlled Trial 504

C.G. Fanelli, S. Pampanelli, F. Porcellati, P. Rossetti, P. Brunetti, and G.B. Bolli

When the goal of insulin therapy in type 1 diabetes mellitus is near-normoglycemia, splitting the evening insulin treatment regimen into short-acting insulin at dinner and neutral protamine Hagedorn (NPH) insulin at bedtime reduces the risks for nocturnal hypoglycemia and hypoglycemia unawareness and decreases the hemoglobin A_{1c} value compared with mixing short-acting insulin and NPH insulin at dinner.

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H.A. Ghofrani, R. Wiedemann, F. Rose, H. Olschewski, R.T. Schermuly, N. Weissmann, W. Seeger, and F. Grimminger

Although limited by the small sample and lack of long-term observations, this study shows that oral sildenafil is a potent pulmonary vasodilator that acts synergistically with inhaled iloprost to cause pulmonary vasodilatation in both severe pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

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A.W. Norris and L.M.B. Laffel

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W. Koenig and M.B. Pepys

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PIER (Physicians' Information and Education Resource), a new information product for the clinician, is now available to American College of Physicians–American Society of Internal Medicine members (http://pier.acponline.org/). PIER represents a new direction in medical publishing because it will help clinicians address complex, multifaceted questions in an informed manner.

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The Appendix for the Information for Authors is published in the first issues of January and July. Please refer to the Appendix for information on manuscript format, style (manuscript typing and assembly), headings in text, style guidelines, title page, abstract, methods and results, discussion and conclusions, references, footnotes, tables and figures, acknowledgments, and current mailing address), and publication (scheduling of papers and proofs, ordering reprints, and complimentary copies).

Annals of Internal Medicine | ARTICLE

Effect of Aerobic Exercise on Blood Pressure: A Meta-Analysis of Randomized, Controlled Trials

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Purpose: **Physical activity has been associated with reduced blood pressure in observational epidemiologic studies and individual clinical trials. This meta-analysis of randomized, controlled trials was conducted to determine the effect of aerobic exercise on blood pressure.**

Data Sources: **English-language articles published before September 2001.**

Study Selection: **54 randomized, controlled trials (2419 participants) whose intervention and control groups differed only in aerobic exercise.**

Data Extraction: **Using a standardized protocol and data extraction form, three of the investigators independently abstracted data on study design, sample size, participant characteristics, type of intervention, follow-up duration, and treatment outcomes.**

Data Synthesis: **In a random-effects model, data from each trial were pooled and weighted by the inverse of the total variance. Aerobic exercise was associated with a significant reduction in mean systolic and diastolic blood pressure (−3.84 mm Hg [95% CI, −4.97 to −2.72 mm Hg] and −2.58 mm Hg [CI, −3.35 to −1.81 mm Hg], respectively). A reduction in blood pressure was associated with aerobic exercise in hypertensive participants and normotensive participants and in overweight participants and normal-weight participants.**

Conclusions: **Aerobic exercise reduces blood pressure in both hypertensive and normotensive persons. An increase in aerobic physical activity should be considered an important component of lifestyle modification for prevention and treatment of high blood pressure.**

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High blood pressure, which affects nearly 50 million Americans, is a serious public health challenge for the United States (1). Cardiovascular disease has been the leading cause of death in the United States for more than 80 years. It is estimated that more than $320 billion is spent annually on the approximately 60 million Americans with cardiovascular disease, for which high blood pressure is an important modifiable risk factor (2). Epidemiologic studies indicate that uncontrolled elevated blood pressure leads to stroke, coronary heart disease, congestive heart failure, and end-stage renal disease (3). Clinical trials have demonstrated that lowering blood pressure reduces incidence of and death from cardiovascular disease (3, 4). These studies also indicate that a decrease of as little as 2 mm Hg in mean diastolic blood pressure in the general population could substantially reduce the risk for disease associated with elevated blood pressure (5).

Physical inactivity is a major risk factor for cardiovascular disease, and persons who are less active and less fit have a 30% to 50% greater risk for high blood pressure (2). Several recent clinical trials have demonstrated that physical activity reduces blood pressure in hypertensive and normotensive persons, independent of weight loss (6–9). However, evidence regarding the magnitude of exercise-related reductions in blood pressure is inconsistent, both in general and among subgroups of the population. Pooling results from individual clinical trials provides more precise and accurate information on the effect of aerobic exercise on blood pressure and allows exploration of variation in intervention effect among subgroups of interest.

METHODS

Study Selection

We conducted a comprehensive literature search of MEDLINE (1966 to September 2001) using the Medical Subject Headings *exercise, physical fitness, hypertension,* and *blood pressure* and the keywords *physical activity* and *aerobic exercise*. We also searched the SPORTDiscus database using the same strategy. In addition, we conducted a manual search by examining reference lists from original research papers and review articles. Initially, three of the authors used predetermined selection criteria to identify and independently review 104 original research reports that included 121 trials. Disagreements were resolved by discussion and, when necessary, by deliberation with a fourth investigator. We included studies that were published in English-language jour-

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Context

Exercise can lower blood pressure, but by how much and in whom?

Contribution

This meta-analysis of 54 trials showed that previously sedentary adults could decrease systolic blood pressure by 3.8 mm Hg (95% CI, 2.7 to 5.0 mm Hg) and diastolic blood pressure by 2.6 mm Hg (CI, 1.8 to 3.4 mm Hg) with regular aerobic exercise.

Exercise lowered blood pressure in people who were normotensive or hypertensive; overweight or of normal weight; and black, white, or Asian.

All frequencies, intensities, and types of aerobic exercise lowered blood pressure.

Cautions

Trials lasting longer than 6 months showed smaller reductions in blood pressure, perhaps because of difficulties in sustaining regular exercise.

—The Editors

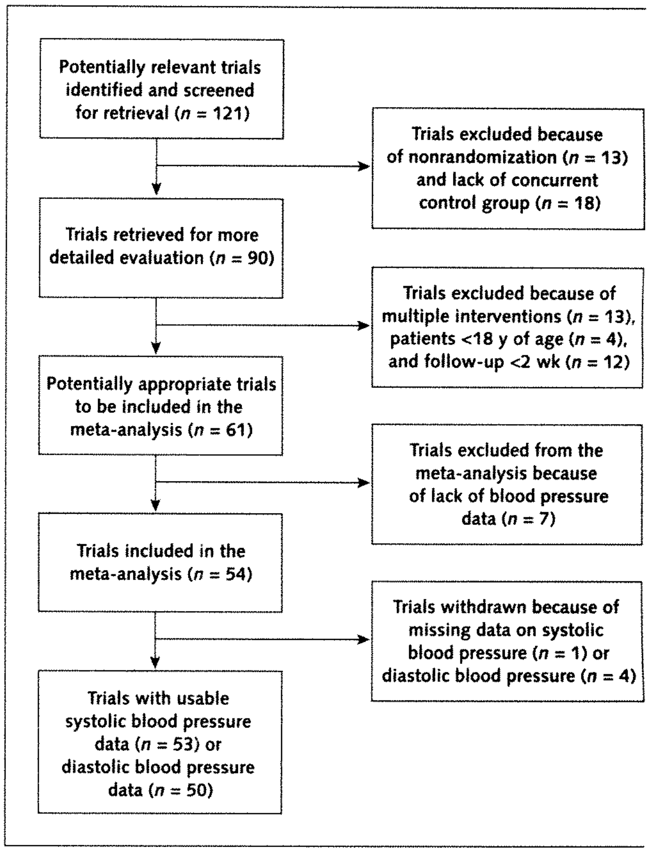
nals; were conducted in persons at least 18 years of age; randomly assigned patients to intervention and concurrent control groups; limited differences between treatment and control groups to aerobic physical activity; lasted for at least 2 weeks; and reported changes in blood pressure (systolic, diastolic, or both) from baseline to follow-up, as well as variances or data to estimate them. Adherence to the program of physical activity and sample size were not defined as inclusion criteria, but their influence on blood pressure reduction was identified as an issue to be investigated. Fifty-four trials (from 38 reports) met the eligibility criteria and were included in the meta-analysis (10–47).

Sixty-seven trials did not meet the eligibility criteria for the meta-analysis (**Figure 1**). The main reasons for exclusion were nonrandomized assignment of the trial participants (13 trials), lack of an appropriate concurrent control group (18 trials), a difference other than aerobic exercise between the active treatment and control groups (13 trials), inclusion of participants younger than 18 years of age (4 trials), a follow-up period of less than 2 weeks (12 trials), and lack of data on blood pressure outcome (7 trials). Results from these trials were not included in the current meta-analysis; a list of excluded clinical trials can be requested from the corresponding author. In addition, 1 trial was missing data on systolic blood pressure and 4 trials were missing data on diastolic blood pressure. These trials, however, were included in analyses of diastolic blood pressure and systolic blood pressure, respectively.

Data Abstraction

Three of the authors used a standardized protocol and reporting form to independently abstract data on characteristics of trial participants and study design, intervention method and duration, and study outcomes. Where unstated, ethnicity was assumed to be white if the study was conducted in Europe, Australia, or New Zealand; Asian if the study was conducted in Asia; and black if the study was conducted in Africa. Differences in duplicate data extraction among the primary reviewers were resolved by discussion and, where necessary, by obtaining additional input from a fourth author.

Figure 1. **Study selection.**


Potentially relevant trials identified and screened for retrieval (n = 121)
Trials excluded because of nonrandomization (n = 13) and lack of concurrent control group (n = 18)
Trials retrieved for more detailed evaluation (n = 90)
Trials excluded because of multiple interventions (n = 13), patients <18 y of age (n = 4), and follow-up <2 wk (n = 12)
Potentially appropriate trials to be included in the meta-analysis (n = 61)
Trials excluded from the meta-analysis because of lack of blood pressure data (n = 7)
Trials included in the meta-analysis (n = 54)
Trials withdrawn because of missing data on systolic blood pressure (n = 1) or diastolic blood pressure (n = 4)
Trials with usable systolic blood pressure data (n = 53) or diastolic blood pressure data (n = 50)

Statistical Analysis

The mean baseline body weight and blood pressure for each trial were calculated by combining mean values from the intervention and control groups, weighted by the number of participants. This mean was not used for calculations of net changes in weight or blood pressure. For parallel and factorial trials, net changes in blood pressure (BP) were calculated as (BP at the end of follow-up in the intervention group − BP at baseline in the intervention group) − (BP at the end of follow-up in the control group − BP at baseline in the control group). For crossover and Latin-square trials, net changes in blood pressure were calculated as BP at the end of the intervention period − BP at the end of the control period.

To pool the overall effect size, we weighted each study by the reciprocal of the total variance for blood pressure change (separate values for systolic and diastolic blood pressure). Variances for net changes in blood pressure were calculated by using confidence intervals, *P* values, *t*-statistics, or individual variances for intervention and control groups (parallel and factorial design) or intervention or control periods (crossover and Latin-square design). For parallel trials that reported variance for paired differences separately for each group, we used standard methods to calculate the pooled variance for net change (48). If the variance for paired differences was not reported, it was calculated by using variances at baseline and at the end of the trial. We used the method of Follmann and colleagues (49), in which a correlation coefficient of 0.5 between initial and final values is assumed. Within each trial, equal variance was assumed between the control and intervention groups, as well as between the beginning and end of the trial.

Fixed-effects and DerSimonian and Laird random-effects models (50) were used to calculate the estimated mean effect of aerobic exercise on blood pressure and associated 95% CIs. Although both models yielded similar results, we chose the random-effects model to present the results because the trials had significant heterogeneity in effect size (50) and were conducted among participants of different ethnic backgrounds, sexes, and hypertensive status, as well as other important covariables.

We performed a series of prestated subgroup analyses to examine the influence of covariables. The subgroups were chosen on the basis of biological plausibility and knowledge of previous studies on the relationship between exercise and blood pressure. For each subgroup, pooled effects were calculated by using the random-effects model and statistical significance was tested by using one-way analysis of variance, weighted by the reciprocal of the total variance for change in blood pressure. Multivariate meta-regression analysis was not performed because many trials did not report important covariables, such as hypertensive status and ethnicity.

We examined the potential for publication bias by using a funnel plot, in which sample size was plotted against net change in blood pressure (51). In addition, a nonparametric "trim and fill" method was used to test and adjust for potential publication bias (52, 53). This method may be used to estimate the number of missing studies that might exist in a meta-analysis and the influence that the missing studies might have had on the estimates of overall effect size.

We used Stata, version 8.0 (Stata Corp., College Station, Texas), for the "trim and fill" method and SAS, version 8 (SAS Institute, Inc., Cary, North Carolina), for all other analyses.

Role of the Funding Source

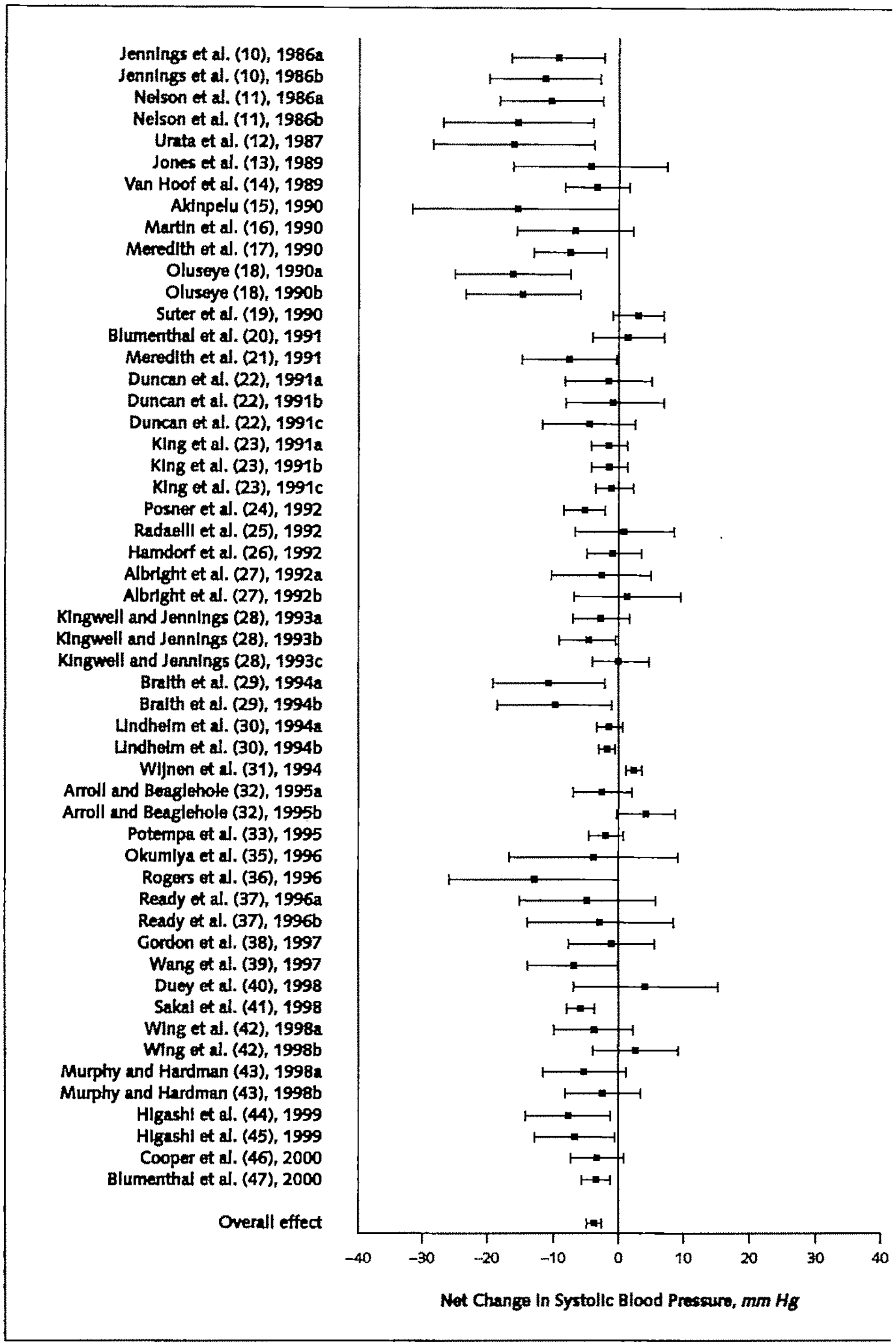
The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Characteristics of the Participants and Study Designs

Characteristics of the 54 trials and their participants are shown in **Appendix Table 1** (available at www.annals.org). The trials were conducted between 1986 and 2000 and varied in size from 8 to 247 participants (median, 28 participants). Overall, 2419 participants were evaluated, but 39 were included twice or three times in separate protocols (10, 11, 28). All trials were conducted in adults (mean age, 21 to 79 years). Of the 51 trials that reported sex distribution, 10 included predominantly (≥80%) men and 17 included predominantly women. Among the 37 trials that reported distribution of ethnicity, all or most of the participants (≥80%) were white in 23 trials, Asian in 6 trials, and black in 4 trials. Fifteen of the 47 trials that reported hypertension status were conducted in hypertensive patients, and 28 were conducted in normotensive participants. Antihypertensive medication was administered in 4 trials in

Figure 2. **Average net change in systolic blood pressure and corresponding 95% CIs related to aerobic exercise intervention in 53 randomized, controlled trials.**



Data on systolic blood pressure were not available in 1 trial (34). Net change was calculated as the difference between the follow-up and baseline blood pressure levels for the intervention and control groups (parallel and factorial trials) or the difference in blood pressure levels at the end of the intervention and control treatment periods (crossover and Latin-square trials). The overall effect represents a pooled estimate obtained by summing the average net change for each trial, weighted by the inverse of its variance.

which all or some of the participants were hypertensive. All 51 trials that reported baseline physical activity were conducted among participants with sedentary lifestyles. The trials varied in length from 3 weeks to 2 years (median duration, 12 weeks). A parallel design was used in 39 trials, a crossover design in 5 trials, a factorial design in 2 trials, and a Latin-square design in 8 trials. All of the trials were open, with the exception of one trial that used a single-blind design (16). In most of the trials, participants in the control groups were instructed not to modify their usual lifestyle, including physical activity. However, in 5 of the trials, participants in the control groups were encouraged to participate in monitored reading, discussion, stretching routines, or a walking program (16, 21, 24, 33, 37).

Average pretreatment blood pressure varied from 101 to 168 mm Hg for systolic blood pressure (median, 126.5 mm Hg) and 61 to 104 mm Hg for diastolic blood pressure (median, 77.0 mm Hg). At baseline, mean body weight varied from 53.4 kg to 99.1 kg (median, 69.3 kg). Mean body mass index at baseline varied from 20.7 kg/m^2 to 36.0 kg/m^2 (median, 25.4 kg/m^2). Net mean change in body weight was available for 38 trials and ranged from −4.1 kg to 1.5 kg (median, −0.3 kg). The net change in mean body weight weighted by sample size (−0.42 kg) did not differ statistically from 0 ($t = -1.76$; $P = 0.09$).

Net Change in Blood Pressure

Fifty-three trials provided information on systolic blood pressure, and 50 trials provided information on diastolic blood pressure. Net change in these variables varied from −16.7 to 3.9 mm Hg and from −11 to 11.3 mm Hg, respectively (**Appendix Table 2**, available at www.annals.org). Systolic blood pressure decreased in 44 of the 53 trials, but the reduction was statistically significant in only 20 (**Figure 2**). Diastolic blood pressure decreased in 42 of the 50 trials, but the reduction was statistically significant in only 16 (**Figure 3**).

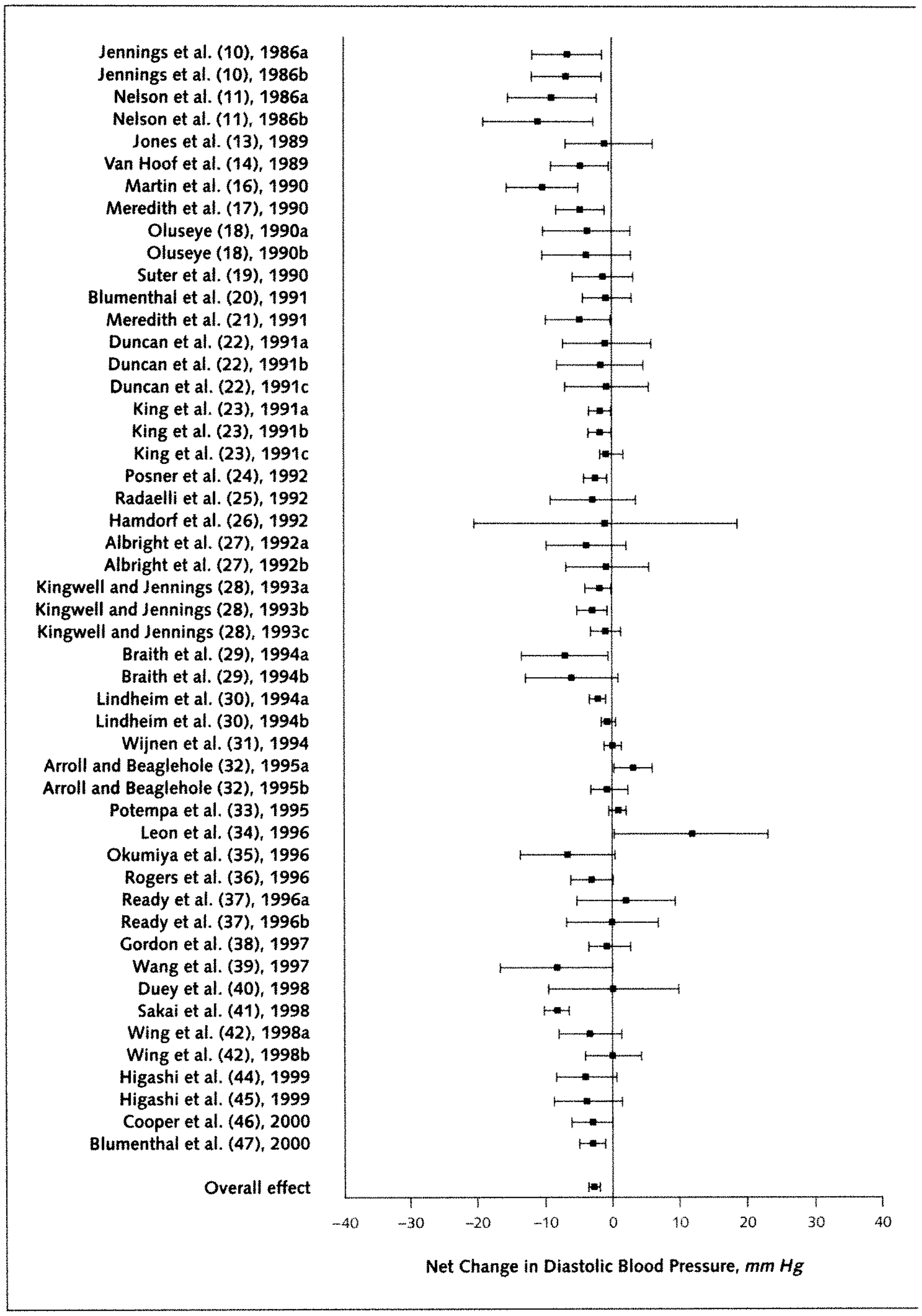
The overall pooled net effect of aerobic exercise on systolic and diastolic blood pressure was −3.84 mm Hg (95% CI, −4.97 to −2.72 mm Hg; $P < 0.001$) and −2.58 mm Hg (CI, −3.35 to −1.81 mm Hg; $P < 0.001$), respectively (**Table 1**). When trials that did not require supervision of the exercise intervention were excluded (19, 25, 27, 31, 44–46), the mean net change in blood pressure increased to −4.13 mm Hg (CI, −5.21 to −3.05 mm Hg; $P < 0.001$) for systolic blood pressure and −2.68 mm Hg (CI, −3.55 to −1.81; $P < 0.001$) for diastolic blood pressure (**Table 1**). After we excluded trials in which antihypertensive medication was administered (25, 32, 33), the mean net change in blood pressure increased to −4.23 mm Hg (CI, −5.42 to −3.05 mm Hg; $P < 0.001$) for systolic blood pressure and −2.91 mm Hg (CI, −3.69 to −2.13 mm Hg; $P < 0.001$) for diastolic blood pressure. After we excluded trials with multiple interventions (25, 30, 32, 38, 42), the net change in blood pressure increased to −4.39 mm Hg (CI, −5.68 to −3.10 mm Hg; $P < 0.001$) for systolic blood pressure and −2.97 mm Hg (CI, −3.82 to −2.12 mm Hg; $P < 0.001$) for diastolic blood pressure. When trials in which blood pressure was not the primary end point were excluded (22–24, 26, 30, 35, 37, 39, 43, 45), the net change in blood pressure

Table 1. **Mean Net Changes in Systolic and Diastolic Blood Pressure according to Different Exclusion Criteria**

Variable	Systolic Blood Pressure			Diastolic Blood Pressure		
	Trials Examined	Net Change (95% CI)	*P* Value	Trials Examined	Net Change (95% CI)	*P* Value
	n	*mm Hg*		*n*	*mm Hg*	
All trials	53	−3.84 (−4.97 to −2.72)	<0.001	50	−2.58 (−3.35 to −1.81)	<0.001
Exercise supervised*	45	−4.13 (−5.21 to −3.05)	<0.001	42	−2.68 (−3.55 to −1.81)	<0.001
Antihypertensive medication not administered†	49	−4.23 (−5.42 to −3.05)	<0.001	46	−2.91 (−3.69 to −2.13)	<0.001
Single intervention between groups‡	47	−4.39 (−5.68 to −3.10)	<0.001	44	−2.97 (−3.82 to −2.12)	<0.001
Blood pressure as primary outcome§	37	−4.39 (−5.93 to −2.86)	<0.001	36	−2.87 (−3.91 to −1.84)	<0.001

* Trials that did not require supervised exercise intervention were excluded (19, 25, 27, 31, 44–46).
† Trials in which antihypertensive medications were administered were excluded (25, 32, 33).
‡ Trials that conducted multiple interventions were excluded (25, 30, 32, 38, 42).
§ Trials in which blood pressure was not the primary outcome were excluded (22–24, 26, 30, 35, 37, 39, 43, 45).

Figure 3. **Average net change in diastolic blood pressure and corresponding 95% CIs related to aerobic exercise intervention in 50 randomized, controlled trials.**



Data on diastolic blood pressure were not available in 4 trials (12, 15, 43). Net change was calculated as the difference between the follow-up and baseline blood pressure levels for the intervention and control groups (parallel and factorial trials) or the difference in blood pressure levels at the end of the intervention and control treatment periods (crossover and Latin-square trials). The overall effect represents a pooled estimate obtained by summing the average net change for each trial, weighted by the inverse of its variance.

increased to −4.39 mm Hg (CI, −5.93 to −2.86 mm Hg; $P < 0.001$) for systolic blood pressure and −2.87 mm Hg (CI, −3.91 to −1.84 mm Hg; $P < 0.001$) for diastolic blood pressure.

Subgroup Analysis

Table 2 summarizes pooled estimates for treatment effect in subgroups of trials defined according to characteristics of participants and study design. Overall, reduced blood pressure was observed in all subgroups. Among the three ethnic groups, black participants had significantly greater reductions in systolic blood pressure and Asian participants had significantly greater reductions in diastolic blood pressure compared with white participants. Trials with the longest follow-up (>24 weeks) had a smaller effect size than trials with short (<10 weeks) or medium (10 to 24 weeks) follow-up. This difference was noted for both systolic and diastolic blood pressure but achieved statistical significance only for the latter. Larger trials (>39 participants) had a statistically significant smaller reduction in blood pressure than smaller trials (22 to 39 or <22 participants). Re-

Table 2. **Mean Net Changes in Systolic and Diastolic Blood Pressure in Subgroups of Trials Defined by Characteristics of Participants and of Study Design***

Characteristic	Systolic Blood Pressure			Diastolic Blood Pressure		
	Studies	Effect Size (95% CI)	*P* Value	Studies	Effect Size (95% CI)	*P* Value
	n	*mm Hg*		*n*	*mm Hg*	
Hypertensive status			>0.2			>0.2
Hypertensive	15	−4.94 (−7.17 to −2.70)		13	−3.73 (−5.69 to −1.77)	
Normotensive	27	−4.04 (−5.32 to −2.75)		26	−2.33 (−3.14 to −1.51)	
Ethnicity			0.03			0.11
White	23	−3.44 (−5.28 to −1.60)		22	−2.61 (−3.82 to −1.40)	
Asian	6	−6.22 (−7.36 to −5.08)		5	−6.58 (−8.44 to −4.72)	
Black	4	−10.96 (−21.02 to −0.89)		2	−3.25 (−7.11 to 0.60)	
Study duration			0.16			0.05
<10 wk	20	−5.15 (−7.44 to −2.85)		17	−4.31 (−6.09 to −2.53)	
10–24 wk	19	−4.62 (−6.90 to −2.34)		19	−2.54 (−3.07 to −2.02)	
>24 wk	14	−2.00 (−3.13 to −0.87)		14	−1.44 (−2.33 to −0.55)	
Sample size			0.004			0.03
<22 participants	17	−6.51 (−9.51 to −3.50)		14	−3.61 (−5.20 to −2.03)	
22–39 participants	17	−5.95 (−7.91 to −3.98)		17	−3.61 (−5.48 to −1.73)	
>39 participants	19	−1.81 (−2.69 to −0.93)		19	−1.31 (−2.06 to −0.56)	
Study design			>0.2			0.18
Parallel or factorial	41	−3.33 (−4.41 to −2.24)		37	−2.23 (−3.10 to −1.35)	
Crossover or Latin square	12	−5.48 (−8.77 to −2.19)		13	−3.68 (−5.42 to −1.94)	
Baseline BMI			>0.2			0.12
<24.5 kg/m²	11	−3.90 (−6.82 to −0.97)		11	−2.38 (−3.69 to −1.06)	
24.5–26.4 kg/m²	12	−4.54 (−7.19 to −1.89)		9	−3.62 (−6.45 to −0.79)	
>26.4 kg/m²	12	−2.17 (−3.30 to −1.03)		12	−1.75 (−2.31 to −1.18)	
Net weight change			>0.2			>0.2
<−1.5 kg	13	−4.76 (−6.19 to −3.33)		10	−3.28 (−5.80 to −0.76)	
−1.5 to 0.2 kg	12	−4.95 (−7.22 to −2.68)		13	−2.91 (−4.86 to −0.97)	
>0.2 kg	12	−2.74 (−4.37 to −1.10)		11	−1.61 (−2.56 to −0.67)	
Exercise type			>0.2			0.16
Bike	17	−5.58 (−8.25 to −2.92)		16	−3.97 (−5.78 to −2.17)	
Walk or jog	23	−2.59 (−3.89 to −1.29)		21	−1.68 (−2.43 to −0.92)	
Mixed or other	13	−3.63 (−6.64 to −1.61)		13	−2.34 (−3.73 to −0.95)	
Exercise frequency			>0.2			>0.2
<120 min/wk	21	−2.82 (−4.22 to −1.43)		21	−2.19 (−3.24 to −1.14)	
120–150 min/wk	15	−4.67 (−7.19 to −2.16)		12	−2.11 (−3.10 to −1.12)	
>150 min/wk	13	−5.13 (−7.64 to −2.61)		13	−2.78 (−3.08 to −1.01)	
Exercise intensity			>0.2			0.18
Low	7	−4.13 (−6.19 to −2.08)		7	−2.71 (−4.05 to −1.36)	
Moderate	28	−4.34 (−5.76 to −2.93)		24	−3.55 (−4.76 to −2.35)	
High	10	−4.00 (−7.06 to −0.94)		11	−1.52 (−2.82 to −0.22)	

* *P* values were obtained by using analysis of variance. BMI = body mass index.

duction in blood pressure was not statistically significantly different among trials in which participants were overweight or of normal weight and lost weight or did not lose weight during the intervention. Reduction in blood pressure was also not statistically significantly different among trials with various types, frequencies, and intensities of exercise intervention.

Publication Bias

A plot of sample size versus effect size for systolic and diastolic blood pressure showed that several large trials reported a moderate reduction in blood pressure (23, 24). However, in a sensitivity analysis using a nonparametric "trim and fill" method, no study was removed and overall effect size remained unchanged.

DISCUSSION

High blood pressure is a major risk factor for stroke, coronary heart disease, congestive heart failure, and end-stage renal disease (2–4). While antihypertensive treatment trials have shown that pharmacologic intervention reduces the risk for cardiovascular and renal disease, concerns have also been raised about the potential for deleterious side effects of antihypertensive drugs (54, 55). As a result, interest in lifestyle modification, including aerobic exercise for the treatment and prevention of hypertension, has increased. Several narrative reviews and meta-analyses have examined the relationship between exercise and blood pressure (6–9). However, previous publications have not systematically reviewed the totality of available evidence and have not explored the influence of important covariables (such as characteristics of study participants, study design, and intervention programs) on change in systolic and diastolic blood pressure.

This meta-analysis is a comprehensive examination of the effect of aerobic exercise on blood pressure and is based on randomized, controlled clinical trials. Our meta-analysis included 54 clinical trials that involved 2419 participants and were conducted in a wide range of geographic regions and ethnic populations. Our study showed that aerobic exercise has an impressive blood pressure–lowering effect: 3.84 mm Hg for systolic blood pressure and 2.58 mm Hg for diastolic blood pressure. Furthermore, the blood pressure reduction associated with aerobic exercise was consistent in sensitivity analyses that included or excluded subgroups of the clinical trials on the basis of study design.

It is important to distinguish between the individual and public health implications of our findings. The blood pressure reduction that we observed may be of moderate interest to practitioners treating individual patients. However, a small decrease in the population's average blood pressure level should dramatically reduce incidence of and death from cardiovascular disease in communities (5).

Our analysis indicates that aerobic exercise lowers blood pressure even in participants whose mean body mass indexes are in the normal range. Indeed, in our meta-analysis, the average overall intervention-related weight change (−0.42 kg) was not statistically significant or biologically important. In addition, our study indicated that mean blood pressure reduction was not significantly associated with mean change in body weight. Instead, blood pressure was significantly reduced even in trials whose participants did not lose weight overall. These findings suggest that the effects of aerobic exercise on blood pressure may be independent of change in body weight.

The blood pressure reduction was not as marked in trials with longer follow-up periods, most likely because participant adherence to the intervention program decreased over time. Study participants were required to participate in exercise sessions supervised by study personnel in all of the short-term trials, while study participants were allowed to exercise independently in longer-term trials. This effect was also noted in individual trials. For example, Wing and coworkers (42) reported a much larger reduction in blood pressure at 6 months than at 2 years. Poor adherence to the intervention program after 6 months, when supervised training was not required, was the most likely explanation (42). Adherence to the intervention program is an essential element for success in achieving and maintaining the maximum benefit of exercise on blood pressure. Our meta-analysis also indicated that blood pressure reduction was smaller in trials with a larger sample size. This may reflect the fact that all of the trials with a large sample size were also longer in duration. In addition, blood pressure was not the primary end point for several of the larger clinical trials (23, 24).

The degree of blood pressure reduction did not differ significantly among trials with different forms of intervention. The blood pressure reduction related to aerobic exercise also did not significantly differ by subgroup according to frequency or intensity of aerobic exercise. Our results, however, indicate that all forms of exercise seem to be effective in reducing blood pressure. Our meta-analysis also suggests that clinical trials that use a crossover or Latin-square design yield a greater reduction in blood pressure than those that use a parallel or factorial design. The elimination of intra-individual variation in trials using crossover or Latin-square design can increase the efficiency of the trial, assuming no carryover effect of exercise on blood pressure. Most crossover or Latin-square trials in our meta-analysis had short interventions and small sample sizes.

Our study has limitations. We could not perform a multivariate meta-regression analysis because data were missing for important covariables, such as ethnicity (17 trials) and hypertensive status (7 trials). We did, however, conduct subgroup analyses based on these important covariables. Aerobic exercise had a slightly greater effect on blood pressure in hypertensive participants than in normotensive participants. The reduction was greater for systolic blood pressure in black persons and for diastolic blood pressure in Asian persons, but only a relatively small number of trials were conducted in persons of these ethnic backgrounds. In addition, all but one trial included in our meta-analysis used an open design. However, many trials masked observers who obtained blood pressure measures. We identified a potential publication bias by funnel-plot method. Several large trials reported a moderate reduction in blood pressure. However, blood pressure was not the primary outcome of interest in most of these trials (23, 26, 30). Furthermore, in a formal test using the "trim and fill" method, reductions in systolic and diastolic blood pressure remained unchanged.

The underlying mechanism or mechanisms responsible for an exercise-induced reduction in blood pressure remain unclear. Recent evidence shows that insulin resistance and hyperinsulinemia may contribute to the pathogenesis of hypertension (56, 57). Clinical trials have shown that aerobic exercise reduces insulin resistance and insulin levels in hypertensive patients (58, 59). Brett and associates (60) have reported that change in blood pressure during exercise is strongly associated with reduction in serum concentrations of total cholesterol and insulin resistance.

In summary, our results suggest that aerobic exercise is an important strategy for prevention and treatment of high blood pressure. We recognize the difficulty of comparing results from meta-analyses conducted on different clinical trials. However, the blood pressure reduction associated with aerobic exercise in our study exceeded that in meta-analyses that explored the corresponding effects of sodium reduction, potassium supplementation, and alcohol reduction on systolic and diastolic blood pressure (61–63). Additional studies are needed to identify ways to improve adherence to exercise. Likewise, the effect of physical activity in ethnic subgroups, especially African-American women, needs further attention.

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Administration of Neutral Protamine Hagedorn Insulin at Bedtime versus with Dinner in Type 1 Diabetes Mellitus To Avoid Nocturnal Hypoglycemia and Improve Control

A Randomized, Controlled Trial

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Background: Intensive insulin treatment of type 1 diabetes mellitus increases the risk for nocturnal hypoglycemia.

Objective: To demonstrate that splitting the evening insulin regimen reduces the risk for nocturnal hypoglycemia in intensive treatment of type 1 diabetes mellitus.

Design: Randomized, open, two-treatment crossover trial in two 4-month periods.

Setting: University research center in Italy.

Patients: 22 C-peptide–negative persons with type 1 diabetes mellitus (mean age [±SD], 29 ± 3 years).

Interventions: Each patient was randomly assigned to one of two insulin regimens for 4 months and then switched to the other regimen for another 4 months. The two treatment regimens were 1) mixed treatment—a mixture of human regular and neutral protamine Hagedorn (NPH) insulin administered before dinner and 2) split treatment—human regular insulin administered at dinner and NPH insulin administered at bedtime.

Measurements: Frequency of nocturnal hypoglycemia. Secondary end points were levels of fasting blood glucose and hemoglobin A_{1c} and responses to experimental hypoglycemia.

Results: During the split-regimen treatment period, patients had fewer episodes of nocturnal hypoglycemia (mean [±SE], 0.10 ± 0.02 episode/patient-day vs. 0.28 ± 0.04 episode/patient-day; $P = 0.002$), a lower fasting blood glucose level (mean [±SE], 7.6 ± 0.2 mmol/L vs. 8.3 ± 0.5 mmol/L [137 ± 4 mg/dL vs. 160 ± 8 mg/dL]; $P = 0.030$), less variable fasting blood glucose levels (SD range, 2.0 ± 0.4 vs. 3.5 ± 0.6; $P = 0.001$), and lower hemoglobin A_{1c} value (mean [±SE], 7.0% ± 0.11% vs. 7.5% ± 0.15%; $P = 0.004$) than during the mixed regimen. Responses to experimental hypoglycemia were better preserved with the split regimen than with the mixed regimen.

Conclusion: When the goal of insulin therapy in type 1 diabetes mellitus is near-normoglycemia, splitting the evening insulin treatment regimen into short-acting insulin at dinner and NPH insulin at bedtime reduces the risks for nocturnal hypoglycemia and hypoglycemia unawareness and decreases the hemoglobin A_{1c} value compared with mixing short-acting insulin and NPH insulin at dinner.

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Nocturnal hypoglycemia is common in patients with type 1 diabetes mellitus (1–7). When insulin treatment is intensified to achieve near-normoglycemia, the frequency of hypoglycemia increases; approximately half of these episodes occur at night (2, 3). Unrecognized nocturnal hypoglycemia is common (1, 3–8). Overtreatment of symptomatic nocturnal hypoglycemia with snacks often results in hyperglycemia the next day (9–11). Asymptomatic nocturnal hypoglycemia can cause morning headache and malaise and may result in diminished awareness, reduced responses of adrenaline, and adaptation of cognitive function during the episode (12–15). Recurrent nocturnal hypoglycemia may contribute to the vicious cycle of hypoglycemia unawareness and impaired hormonal counterregulation in patients with type 1 diabetes, leading to increased risk for severe hypoglycemia (16).

The nonphysiologic pharmacokinetics and pharmacodynamics of insoluble, intermediate-acting insulin preparations, such as neutral protamine Hagedorn (NPH) insulin, play a central role in inducing nocturnal hypoglycemia in type 1 diabetes (4). When injected at dinner, NPH insulin results in excess plasma insulin bioavailability at approximately midnight, a time at which patients with type 1 diabetes are more insulin sensitive (17, 18); thus, the risk for hypoglycemia increases between midnight and 3:00 a.m. Later, insulin deficiency develops at dawn (4, 18) and contributes to fasting hyperglycemia. When the nocturnal peak plasma level of insulin produced by an evening injection of in-

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termediate-acting (NPH) insulin is postponed by 3 to 4 hours as a result of injecting NPH insulin at bedtime instead of at dinner, fasting and postbreakfast blood glucose levels decrease (19).

Although the pharmacokinetics and pharmacodynamics of NPH insulin would suggest that splitting of the evening insulin regimen (administering short-acting insulin at dinner and NPH insulin at bedtime) should decrease the risk for nocturnal hypoglycemia, to the best of our knowledge no data indicate this in patients with type 1 diabetes mellitus. We tested the hypothesis that in intensive treatment of type 1 diabetes, splitting the evening insulin administration rather than mixing short-acting and NPH insulin at dinner reduces the risk for nocturnal hypoglycemia and improves glycemic control, awareness of hypoglycemia, and counterregulation to hypoglycemia.

Context

Clinicians often split evening insulin dosing (short-acting insulin at dinner and long-acting insulin at bedtime rather than both types with dinner) to avoid nocturnal hypoglycemia in patients with type 1 diabetes mellitus.

Although split dosing makes sense theoretically, no rigorous studies have examined its effects on glycemic control.

Contribution

In this randomized, controlled crossover trial, episodes of nocturnal hypoglycemia were less frequent and fasting blood glucose and hemoglobin A_{1c} levels were lower with split evening insulin than with mixed dosing at dinner.

Clinical Implications

This study supports splitting evening insulin dosing to improve glycemic control in patients with intensively treated type 1 diabetes.

–The Editors

METHODS

Patients

We recruited 22 patients (10 women, 12 men; mean age [±SD], 29 ± 3 years) with type 1 diabetes mellitus (mean duration of diagnosed diabetes [±SD], 14 ± 2 years) receiving long-term intensive insulin treatment (multiple insulin injections with regular human insulin before meals and NPH insulin at bedtime) from the outpatient Diabetes Clinic of the Department of Internal Medicine at the University of Perugia. At baseline, the mean (±SD) body mass index of the cohort was 23 ± 1 kg/m^2, and the mean (±SD) hemoglobin A_{1c} value was 6.7% ± 0.4%. Patients had no detectable microangiopathic complications; autonomic neuropathy, as assessed by using a standard battery of cardiovascular tests (20); peripheral neuropathy; or microalbuminuria. The patients had no history or clinical evidence of hypertension and were taking no medications other than insulin. We excluded 1) patients with hypoglycemia unawareness, defined as an absence of symptoms while the blood glucose level is approximately 2.5 to 2.8 mmol/L (45 to 50 mg/dL) and 2) patients with a history of severe hypoglycemia, defined as episodes of hypoglycemia requiring assistance from another person in the previous year. All patients in the study gave informed consent. The Institutional Review Board of University of Perugia in Perugia, Italy, approved this study.

Study Design

After a 1-month run-in period, during which patients continued their usual regimen of multiple daily insulin injections, we randomly assigned patients to receive one of the two following treatment regimens for the first 4-month treatment period: 1) a continued regimen of four daily insulin injections (evening split treatment)—that is, administration of regular insulin before dinner and NPH insulin at bedtime (usually between 10:30 p.m. and 11:00 p.m.) or 2) a regimen of regular insulin at breakfast and lunch and a mixture of regular and NPH insulins at dinner (evening mixed treatment). Thereafter, the patients were switched to the other treatment for an additional 4 months. Insulin (short-acting and NPH) was administered with syringes to achieve the target values for fasting blood glucose of 5.0 to 6.7 mmol/L (90 to 120 mg/dL) before meals and at bedtime (2). The dose of mealtime regular insulin was titrated on the basis of the blood glucose measurement obtained 1) before the meal and 2) on the previous day, 4 to 5 hours after that meal, or, in the case of the evening meal, at bedtime. The dose of NPH insulin given at dinner or at bedtime was titrated on the basis of the predinner or bedtime blood glucose level, respectively.

The patients were instructed to measure capillary blood glucose levels by using Reflolux S (Boehringer Mannheim, Mannheim, Germany) before each insulin

Table 1. **Insulin Dosing during the Two Treatment Periods of the Study***

Treatment Regimen and Insulin Type	Dose			
	Breakfast	Lunch	Dinner	Bedtime
	←	IU		→
Evening split administration				
Short-acting	5 ± 0.6	9 ± 1.0	9 ± 1.4	–
NPH	–	–	–	12 ± 2.4
Evening mixed administration				
Short-acting	7 ± 0.7	10 ± 1.2	8 ± 1.1	–
NPH	–	–	10 ± 2.0	–

* Insulin doses are expressed as the mean ± SE. NPH = neutral protamine Hagedorn.

injection, at bedtime, and every other day at 3:00 a.m. The patients were also asked to skip no more than one of their daily capillary glucose measurements and to keep diaries of blood glucose values, insulin dosage, and hypoglycemic episodes (blood glucose level ≤4.0 mmol/L [≤72 mg/dL]) occurring any time during the day.

To prevent nocturnal hypoglycemia, the patient instructions included a suggestion to consume a snack containing approximately 20 g of carbohydrates (approximately 20 g of bread and approximately 60 mL of 2% milk) when the capillary blood glucose level at bedtime was less than 7.0 mmol/L (<126 mg/dL) with the evening mixed treatment and less than 6.0 mmol/L (<108 mg/dL) with the evening split treatment. We also suggested that patients have a similar snack if the blood glucose level at 3:00 a.m. was 4.0 mmol/L or less (≤72 mg/dL) at any time during the night. If such a snack did not relieve hypoglycemic symptoms in approximately 10 minutes, patients were told to have another snack (for a total of 40 g of carbohydrates). Throughout the study, patients visited the outpatient clinic monthly to submit their diaries and had frequent telephone contacts (every 3 to 6 days) with the investigators.

At the end of each treatment period, patients were admitted to the clinical research unit of the hospital, where blood glucose was monitored overnight; the next morning, counterregulatory and symptomatic responses to hypoglycemia and cognitive performance were evaluated during a hyperinsulinemic, stepped hypoglycemic clamp study. Hemoglobin A_{1c} values were measured before randomization and at the end of both treatment periods.

In-Hospital Evaluation

Overnight Testing

Patients were admitted for overnight evaluations after dinner (and, thus, after premeal insulin administration), at approximately 9:00 p.m. A hand vein of the nondominant arm was cannulated retrogradely, and the hand was maintained in a hot pad (approximately 60 °C) for sampling of arterialized-venous blood (21). A second venous line of the ipsilateral arm was cannulated for intravenous infusion of glucose whenever an infusion was needed to prevent hypoglycemia (that is, to prevent a decrease in plasma glucose level to ≤4.0 mmol/L [≤72 mg/dL]). Glucose was infused whenever the plasma glucose level decreased to less than 4.4 mmol/L (<80 mg/dL). On overnight stays, patients were allowed to watch television until 11:00 p.m., at which time patients receiving the evening split regimen had their bedtime injection of NPH insulin. Overnight, patients gave blood samples for measurement of plasma glucose and insulin levels every 30 minutes.

Stepped Hypoglycemic Clamp Studies

At 8:30 a.m. on the following morning, a variable intravenous infusion of human regular insulin (diluted to 1 U/mL in 2 mL of the patient's blood and sodium chloride [NaCl 0.9%] to a final volume of 100 mL) was begun to maintain a plasma glucose level of 5.0 mmol/L (90 mg/dL). Infusion continued until 10:00 a.m. For this procedure, which was done according to a previously described algorithm (22), we used an intravenous syringe pump (Harvard Apparatus, Ealing, South Natick, Massachusetts). At 10:00 a.m., the rate of intravenous insulin infusion was increased to 1 $mU/kg^{-1} \cdot min^{-1}$ until 2:30 p.m. (270 minutes), followed by 2 $mU/kg^{-1} \cdot min^{-1}$ for an additional 90 minutes, until 4:00 p.m. (time, 360 minutes). Plasma glucose was clamped by variable glucose infusion at sequential target glucose values of 4.3, 3.7, 3.0, and 2.3 mmol/L (78, 66, 54, and 42 mg/dL); at each target level, blood was drawn to measure hormone and metabolite levels, and patients were assessed for symptoms of hypoglycemia and for cognitive function (23–25).

Symptoms were quantified by asking the patients to score (on a scale in which 0 = none and 5 = severe) each of the following symptoms: dizziness, tingling, blurred vision, difficulty in thinking, faintness, anxiety, palpitations, hunger, sweating, irritability, and tremor. The first five symptoms were considered neuroglycopenic and the last six, autonomic. The sum of each of these constituted the symptom score.

Analytic Methods

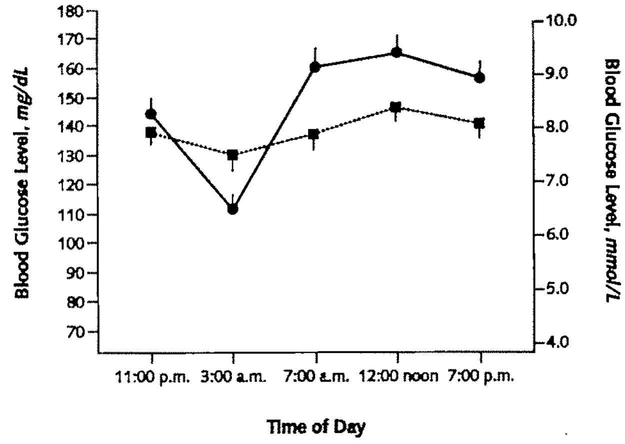
We measured plasma glucose levels using a Beckman glucose analyzer (Glucose Analyzer II, Beckman Instruments, Fullerton, California). In addition, we measured levels of plasma insulin, growth hormone, cortisol, adrenaline and noradrenaline, free fatty acids, glycerol, β-hydroxy butyric acid (β-OH-butyrate), and alanine and lactate by using previously described assays (26–31); pancreatic polypeptide values were measured by using EURIA-PP (Pancreatic Polypeptide Radioimmunoassay, Malmö, Sweden) (32). To remove antibody-bound insulin, plasma was mixed with an equal volume of 30% polyethylene glycol immediately after blood collection (27). Hemoglobin A_{1c} values were determined by high-performance liquid chromatography by using HI-Auto A_{1c} TM HA 8121 apparatus (DIC, Kyoto Daiichi, Kogaku Co., Ltd., Kyoto, Japan) (range in nondiabetic patients, 3.8% to 5.5%).

Statistical Analysis

Sample-size power calculations indicated that we would require 20 patients to detect a 50% decrease in the primary end point with a power of 80% at the 0.05 significance level. Therefore, we enrolled 22 patients, allowing for a maximum of 2 participants to withdraw from the study.

All patients completed the study. For the statistical analyses, we used patient data from the final month of each treatment period. To determine carryover and treatment effects, we used a two-period crossover analysis of variance, with participants, treatment period, and type of treatment regimen included in the model (33). We observed no evidence of statistically significant carryover effects. The maximum and minimum concentration, the time of maximum and minimum concentration for counterregulatory hormone levels, and the maximum score for hypoglycemic symptoms were read directly from the raw data. Data from cognitive tests were standardized to Z scores, according to the following formula: $Z = (x - M)/SD$, where x is the original score, and M and SD are the mean and standard deviation of the x scores at baseline (34). Z scores were analyzed by repeated-measures analysis of variance (35). Z scores are presented as the mean of the Z scores for all tests administered. Glycemic thresholds for hormone release were calculated as the plasma glucose level at which a given response increased by 2 SDs above basal values, whereas glycemic thresholds for symptoms were calculated as the plasma glucose level at which the symptom score increased by at least three points above baseline. We compared the frequency of nocturnal hypoglycemia between the two treatments by using the McNemar test (33, 36). Finally, we performed a regression analysis according to the least-squares method (36). We present data in the text and tables as the mean (±SE), except as otherwise indicated; we considered differences to be statistically significant if the P value was 0.05 or less. We conducted the statistical analyses by using NCSS 2000 software (Number Cruncher Statistical System, Kaysville, Utah).

Figure 1. **Mean (±SE) daily blood glucose levels in 22 patients during insulin regimens of evening split administration (*squares*) and evening mixed administration (*circles*).**



The figure shows overall data from home monitoring during the final month of treatments.

Table 2. **Blood Glucose Control during the Last Month of Each Treatment Period***

Variable	Treatment Period		Difference Estimate (95% CI)	*P* Value
	Mixed-Insulin Administration	Split-Insulin Administration		
Frequency of self-treated nocturnal hypoglycemic episodes, *n/patient-day*†	0.28 ± 0.04	0.10 ± 0.02	−0.18 (−0.27 to −0.07)	0.002
Mean daily blood glucose level, *mmol/L [mg/dL]*	8.3 ± 0.3 [150 ± 5.4]	7.7 ± 0.2 [139 ± 3.6]	−0.6 (−4.3 to −0.1) [−10.8 (−77 to −1.8)]	0.038
SD of fasting blood glucose values, *mmol/L [mg/dL]*	3.5 ± 0.6 [63 ± 11]	2.0 ± 0.4 [36 ± 7]	−1.5 (−2.1 to −1.0) [−27 (−38 to −18)]	0.001
Hemoglobin A_{1c} value, %	7.5 ± 0.15	7.0 ± 0.11	−0.5 (−0.81 to −0.18)	0.004

* Values expressed with the plus/minus sign are the mean ± SE.
† Hypoglycemia was defined as a blood glucose level less than 4.0 mmol/L (<72 mg/dL).

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RESULTS

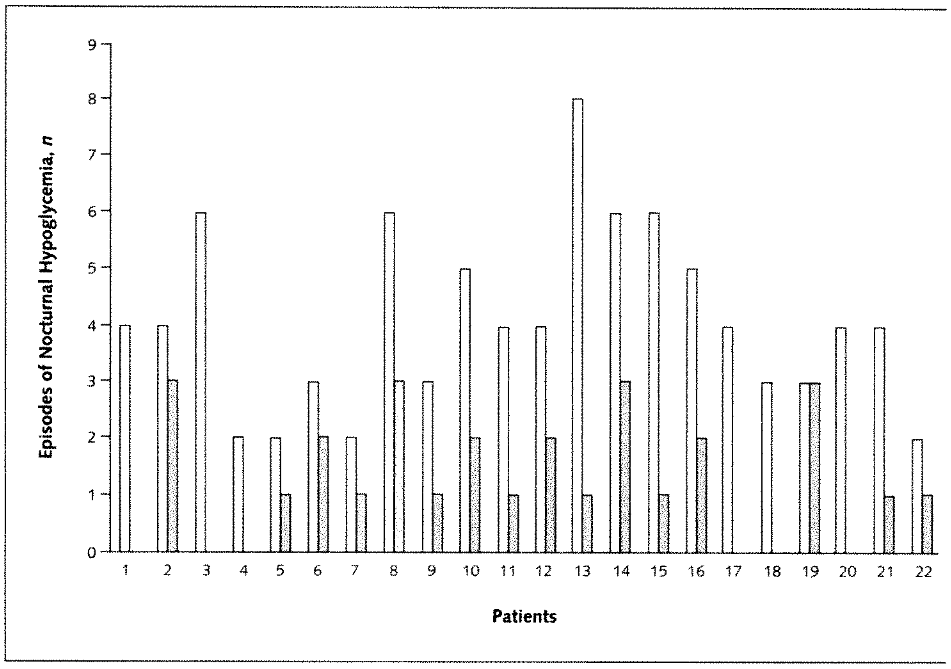
Insulin Doses

During the final month of the treatment periods, the total daily insulin doses in the split and mixed regimens did not differ (35 ± 2 IU/d vs. 35 ± 2.5 IU/d, respectively; $P > 0.2$) (**Table 1**).

Glycemic Control

Figure 1 shows the daily home-monitored blood glucose levels. We collected 2890 total measurements (131.4 ± 0.2 measurements/patient) of blood glucose from the last month of mixed insulin treatment and 2879 measurements (130.9 ± 0.23 measurements/patient) from the last month of split treatment ($P = 0.113$). The mean blood glucose level at 3:00 a.m. was

Figure 2. **Number of nocturnal hypoglycemia episodes in each patient (*n* = 22) during the final month of each treatment period—mixed (*white bars*) versus split (*shaded bars*) administration of evening insulin.**

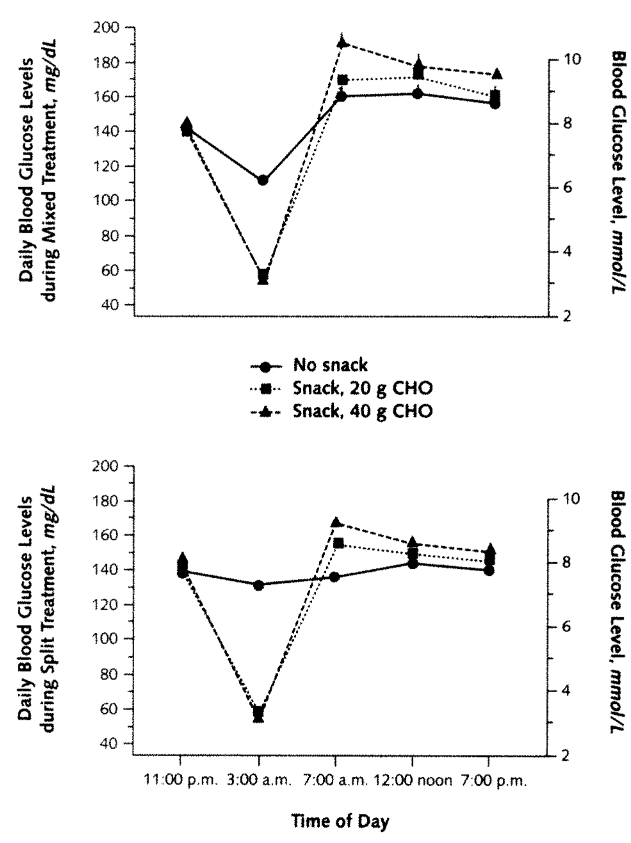


6.2 ± 0.2 mmol/L (111 ± 4 mg/dL) during the mixed-treatment period and 7.2 ± 0.2 mmol/L (130 ± 4 mg/dL) during split treatment ($P < 0.001$). The frequency of hypoglycemia at 3:00 a.m. was greater in the mixed-treatment period than in the split-treatment period (0.28 ± 0.04 episode/patient-day vs. 0.10 ± 0.02 episode/patient-day, respectively; $P = 0.002$) (**Table 2**). On average, each patient experienced 2.8 (95% CI, 1.9 to 3.7) fewer episodes of hypoglycemia with split than with mixed dosing (**Figure 2**). No episodes of severe hypoglycemia occurred in either group. Blood glucose levels were greater with mixed than with split treatment at fasting (8.9 ± 0.5 mmol/L vs. 7.6 ± 0.2 mmol/L [160 ± 8.3 mg/dL vs. 137 ± 3.9 mg/dL]), before lunch (9.2 ± 0.4 mmol/L vs. 8.1 ± 0.2 mmol/L [165 ± 6.7 mg/dL vs. 146 ± 3.1 mg/dL]), and before dinner (8.7 ± 0.4 mmol/L vs. 7.8 ± 0.3 mmol/L [156 ± 7.0 mg/dL vs. 141 ± 4.9 mg/dL]); however, the differences between treatments were statistically significant only for measurements obtained at fasting ($P = 0.030$) and before lunch ($P = 0.050$) ($P = 0.083$ for predinner measurements).

Overall, 308 and 301 blood glucose values were collected at 3:00 a.m. from the mixed- and split-treatment periods, respectively. The number of hypoglycemic values recorded was 90 (29%) and 28 (9.3%) in the mixed- and split-treatment periods, respectively (odds ratio, 3.1 [CI, 2 to 5]; $P < 0.001$). During the mixed- and split-treatment periods, 36 of 90 hypoglycemic episodes (40%) and 16 of 28 episodes (57%), respectively, were corrected by consuming 20 g of carbohydrates and 54 episodes (60%) and 12 episodes (43%), respectively, were corrected by consuming 40 g of carbohydrates. In both the mixed- and split-treatment periods, the fasting blood glucose levels were greater after a 3:00-a.m. episode of hypoglycemia treated with carbohydrate ingestion than after a hypoglycemia-free night (with no carbohydrate ingestion) (**Figure 3**).

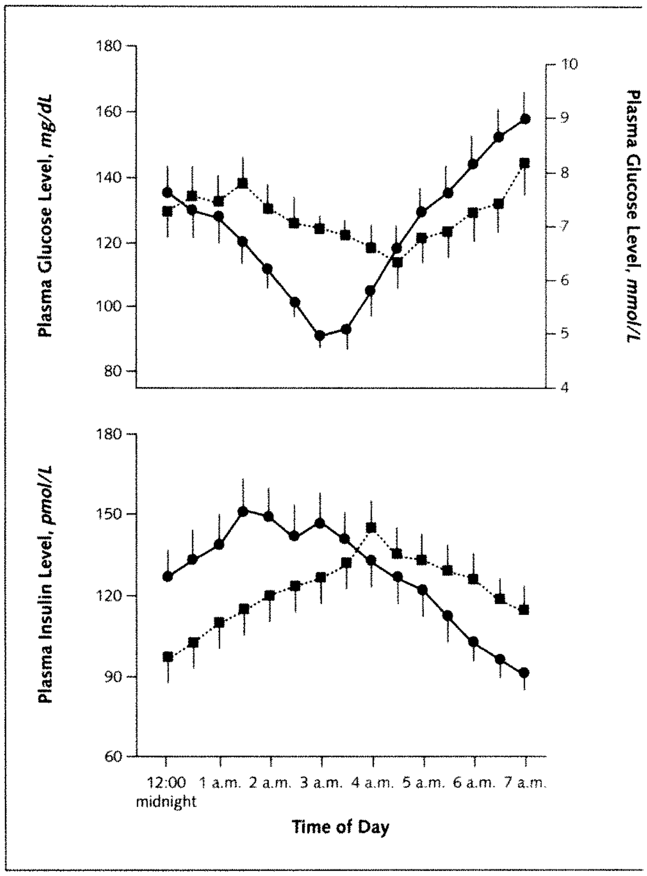
Multiple regression analysis showed a robust relationship between the amount of carbohydrate ingested to correct nighttime hypoglycemia and the fasting blood glucose level in the mixed-treatment ($R^2 = 68.8\%$; $P < 0.001$) and split-treatment ($R^2 = 42\%$; $P = 0.007$) periods. In contrast, nocturnal blood glucose values correlated weakly with fasting blood glucose values in the mixed-treatment period ($R^2 = 18.5\%$; $P = 0.046$) and did not correlate in the split-treatment period ($R^2 = 0.17\%$; $P > 0.2$). Independent of treatment, 55% of the variation in fasting plasma glucose levels was explained by carbohydrate ingestion and only 9.4% was explained by low blood glucose levels. However, the fasting blood

Figure 3. **Mean (±SE) daily blood glucose levels (home-monitored during the final month of both treatments).**



The daily glucose levels are categorized according to hypoglycemia status and resultant snack consumption at the 3:00-a.m. measurement: no hypoglycemia (glucose level > 4.0 mmol/L [>72 mg/dL]) with no snack; hypoglycemia (glucose level ≤ 4.0 mmol/L [≤72 mg/dL]) with 20-g carbohydrate (*CHO*) snack; or hypoglycemia with 40-g CHO snack. **Top.** Evening mixed-treatment period: Patients received a mixture of human regular insulin and neutral protamine Hagedorn (NPH) insulin before dinner. During this treatment period, the following numbers of nocturnal glucose measurements were obtained: for nonhypoglycemia nights with no snack, *n* = 218; for hypoglycemia nights with 20-g CHO snack, *n* = 36; for hypoglycemia nights with 40-g CHO snack, *n* = 54. **Bottom.** Evening split-treatment period: Patients split the evening insulin regimen into human regular insulin administration before dinner and NPH insulin administration at bedtime. During this treatment period, patients recorded the following numbers of nocturnal glucose measurements: for nonhypoglycemia nights with no snack, *n* = 273; for hypoglycemia nights with 20-g CHO snack, *n* = 16; for hypoglycemia nights with 40-g CHO snack, *n* = 12.

Figure 4. **Mean (±SE) levels of plasma glucose (*top*) and insulin (*bottom*) during overnight hospitalization with evening regimen of split insulin (*squares*) versus mixed insulin (*circles*) administration.**



Fifteen patients during the mixed-treatment period required glucose infusion between 2:00 a.m. and 4:00 a.m. to prevent a decrease in plasma glucose level to 4.0 mmol/L or less (≤72 mg/dL).

glucose level was lower with split than with mixed treatment, both after a nonhypoglycemic night and after a hypoglycemic night corrected with 20 g or 40 g of carbohydrates ($P < 0.05$). Our finding was similar for blood glucose level measured before lunch after nights with and without hypoglycemic episodes (with 20-g or 40-g carbohydrate consumption) ($P < 0.05$). Predinner blood glucose values did not differ. The percentage of fasting blood glucose measurements in the target range was 15% with mixed treatment and 28% with split treatment.

Symptomatic nocturnal hypoglycemia (episodes during which patients spontaneously awoke because of symptoms and that were confirmed by a blood glucose value ≤ 4.0 mmol/L [≤72 mg/dL] between 2:00 a.m. and 7:00 a.m.) was more frequent with mixed than with split treatment (0.045 ± 0.005 episode/patient-day vs. 0.027 ± 0.003 episode/patient-day; $P = 0.005$). Blood glucose levels during hypoglycemic episodes were lower with mixed than with split treatment (glucose level, 2.7 ± 0.1 mmol/L vs. 3.0 ± 0.1 mmol/L [48.8 ± 1.1 mg/dL vs. 53.8 ± 1.4 mg/dL]; $P = 0.014$). Mean values for daily blood glucose, hemoglobin A_{1c}, and the variability of fasting blood glucose (37) were all greater with mixed than with split treatment (**Table 2**). We observed no difference in the rate of diurnal hypoglycemia between treatments (data not shown).

In-Hospital Control of Nocturnal Plasma Glucose Levels

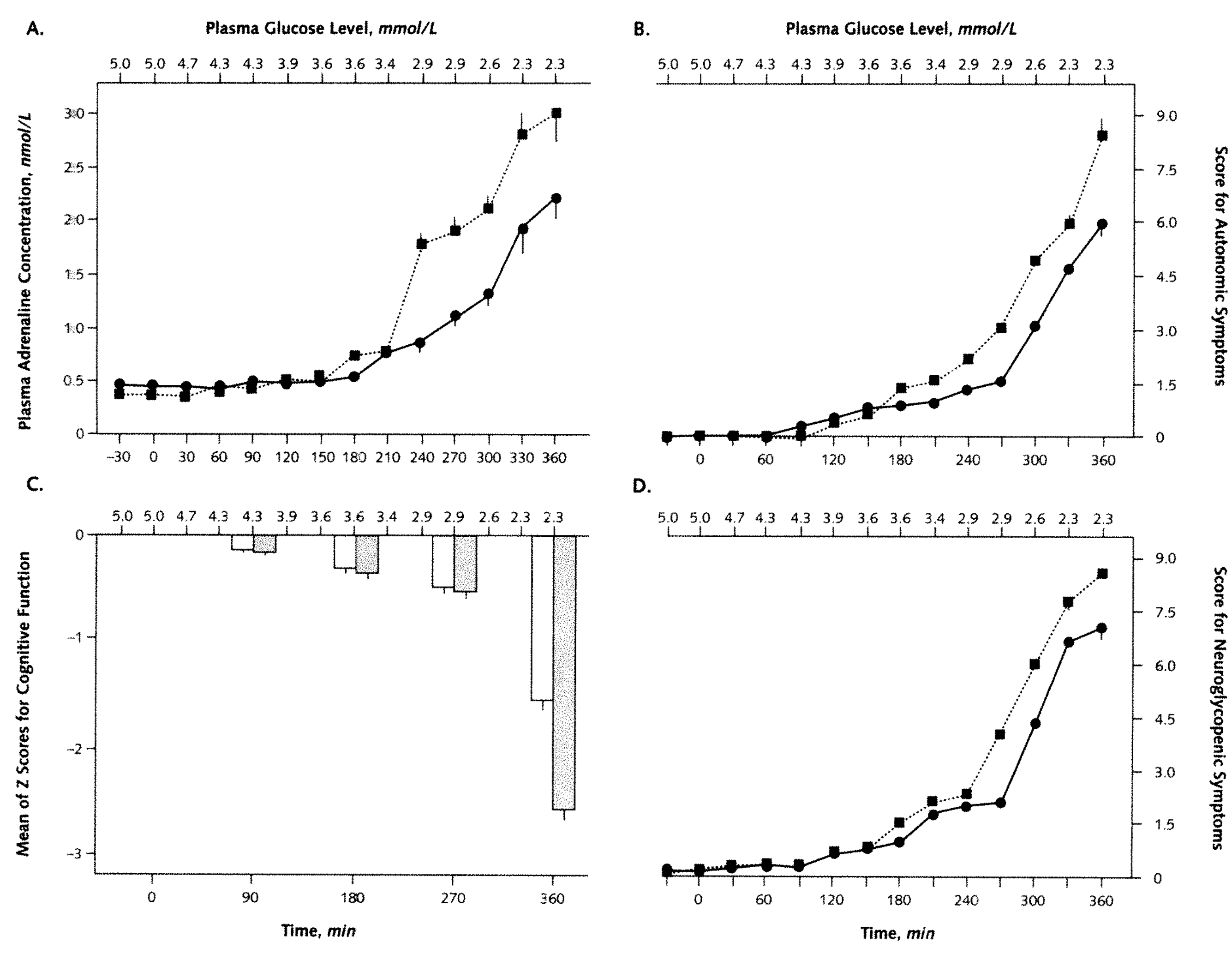
Plasma glucose levels decreased to a nadir of 5.0 ± 0.2 mmol/L (91 ± 4 mg/dL) at 3:00 a.m. in the mixed-treatment period (**Figure** 4) and to 6.1 ± 0.1 mmol/L (110 ± 2 mg/dL) at 4:30 a.m. in the split-treatment period ($P < 0.001$). At 7:00 a.m., the plasma glucose level was greater during mixed than during split treatment, although the difference was not statistically significant. Of the 22 patients studied, plasma glucose levels obtained between 3:00 a.m. and 4:00 a.m. decreased to 4.4 mmol/L or less (≤80 mg/dL) in 18 patients during the mixed-treatment period and in 4 patients during the split-treatment period. Fifteen patients during mixed treatment compared with no patients during split treatment required glucose infusion between 2:00 a.m. and 4:00 a.m. to prevent hypoglycemia.

The plasma insulin level at 12:00 midnight was greater during mixed than during split treatment (131 ± 53 pmol/L vs. 94 ± 34 pmol/L; $P = 0.011$) and reached a peak of 151 pmol/L at 1:30 a.m. Thereafter, the plasma insulin level decreased to 90 pmol/L by 7:00 a.m. During split treatment, the plasma insulin level increased to a peak of 144 pmol/L at 4:00 a.m. Thereafter, at 7:00 a.m., the plasma insulin level was still greater than during mixed treatment (113 ± 25 pmol/L vs. 90 ± 16 pmol/L, respectively; $P = 0.024$).

Effects on Awareness of, Counterregulation to, and Cognitive Function during Stepped Hypoglycemia

Plasma insulin level was 672 ± 60 pmol/L between 0 and 270 minutes and 888 ± 132 pmol/L between 270 and 360 minutes, with no difference between treatments. Plasma glucose level was successfully clamped at nominal values (given in the Methods section), with no differences between treatments (data not shown). Plasma glucagon responses were similarly suppressed during hypoglycemia in both the mixed- and split-treatment periods, and plasma pancreatic polypeptide concentrations also were similar in both treatment periods (data not shown). Plasma adrenaline concentrations increased earlier and to a greater extent in the split-treatment period than in the mixed-treatment period (**Figure 5**). The plasma glucose thresholds for adrenaline level were 3.4 ± 0.1 mmol/L (62 ± 0.66 mg/dL) during split treatment and 3.3 ± 0.1 mmol/L (59.82 ± 0.62 mg/dL) during mixed treatment ($P = 0.013$), and the peak plasma adrenaline concentrations were 3.0 ± 0.25 nmol/L and 2.1 ± 0.20 nmol/L, respectively ($P = 0.045$). Plasma concentrations of free fatty acids, glycerol, alanine, lactate, and β-OH-butyrate did not differ between the two treatments.

Figure 5. **Various assessments during stepwise, insulin-induced, clamped hypoglycemia in patients with type 1 diabetes mellitus (*n* = 22) during two treatment periods—evening split insulin administration (*squares, shaded bars*) and evening mixed administration (*circles, white bars*).**



A. Plasma adrenaline concentration. B. Score of autonomic symptoms. C. Mean of *Z* scores of cognitive function. D. Score of neuroglycopenic symptoms. Standard error bars are shown. To convert the top x-axis values (in mmol/L)—which represent induced, approximate target levels of plasma glucose—to mg/dL, divide by 0.0555.

Autonomic symptom scores increased earlier with split treatment than with mixed treatment (plasma glucose thresholds, 3.0 ± 0.1 mmol/L [54 ± 0.81 mg/dL] and 2.9 ± 0.1 mmol/L [51.5 ± 0.68 mg/dL], respectively; $P = 0.010$); these scores had increased by the end of the treatment periods (symptom score, 8.6 ± 0.91 in the split-treatment period vs. 6.0 ± 0.82 in the mixed-treatment period; $P = 0.026$) (**Figure 5**). The glycemic threshold was similar for neuroglycopenic symptoms (2.9 ± 0.1 mmol/L [52.2 ± 0.72 mg/dL] vs. 2.8 ± 0.1 mmol/L [51.8 ± 0.53 mg/dL]; $P > 0.2$); in contrast, the maximal response tended to be greater for split treatment (score, 8.8 ± 0.7 vs. 7.3 ± 0.5), although the difference between treatments was not statistically significant ($P = 0.071$). Cognitive function deteriorated in both treatment groups during hypoglycemia ($P < 0.001$); however, by the end of the testing, deterioration was greater for split treatment than for mixed treatment (mean of Z scores, −2.6 ± 0.4 vs. −1.6 ± 0.2; $P = 0.035$) (**Figure 5**).

DISCUSSION

First, these data demonstrate that in intensive treatment of type 1 diabetes, splitting the evening administration of insulin to short-acting insulin at dinner and NPH insulin at bedtime has several advantages over simultaneous (mixed) administration of short-acting and NPH insulins at dinner. Compared with mixed treatment, evening split treatment reduced by more than 60% the risk for nocturnal hypoglycemia; improved long-term control of blood glucose levels (hemoglobin A_{1c} levels were approximately 0.5% lower); decreased variability of blood glucose levels in the fasting state; and preserved better hormonal, symptom, and cognitive function responses to hypoglycemia. We conclude that, whenever possible, patients with type 1 diabetes should be given the split insulin regimen in the evening.

To the best of our knowledge, Francis and colleagues (19) were the first to propose splitting evening insulin to decrease fasting and postbreakfast blood glucose levels. However, their study identified no differences in the risk for nocturnal hypoglycemia or in long-term blood glucose control (as determined by hemoglobin A_{1c} values).

We monitored patients overnight in the hospital to clarify the mechanisms of less frequent nocturnal hypoglycemia with split insulin treatment compared with mixed treatment. The benefits of split treatment appear to be mediated by the dynamics of overnight plasma insulin levels—that is, less insulinization immediately after midnight with less insulin waning at dawn (4)—as previously reported (5, 19).

Second, long-term glycemic control was better with the evening split than with mixed insulin administration. This is probably the long-term result of greater hyperglycemia in the fasting state due to more rapid insulin waning and greater day-long hyperglycemia after correction of nocturnal hypoglycemia with snacks in the mixed regimen (**Figure 4**). Of note, hyperglycemic episodes after hypoglycemia were prolonged because blood glucose levels were still greater at lunch after a hypoglycemic night than after a nonhypoglycemic night, despite an increased dose of regular insulin administered at breakfast. However, patients experienced less fasting and prelunch hyperglycemia after nocturnal hypoglycemia during split treatment than during mixed treatment. In addition, fasting blood glucose levels varied less with split treatment, possibly because of the lower frequency of nocturnal hypoglycemia and greater levels of plasma insulin at that time of day in the split-treatment group.

Third, our data indicate that split treatment preserves hormonal counterregulation (except glucagon), and leads to better hypoglycemia awareness (both autonomic and neuroglycopenic symptoms). The improvement involved not only maximal responses but also plasma glucose thresholds of responses, although the difference of the latter was rather small for adrenaline and was not statistically significant for neuroglycopenic symptoms. Thus, plasma adrenaline levels and autonomic symptoms increased for a lower decrement in plasma glucose in split compared with mixed treatment, suggesting that patients responded earlier to hypoglycemia during the split-treatment period. Because the frequency of diurnal hypoglycemia was similar between treatments, less frequent nocturnal hypoglycemia was probably related to the better responses to hypoglycemia observed with split versus mixed treatment. Support for such an interpretation derives from studies comparing responses before and after induction of nocturnal hypoglycemia (14, 15) and from observations before and after prevention of hypoglycemia (38).

Despite the heterogeneity of responses to NPH insulin due to variability among patients, our findings strongly indicate that physicians should consider splitting evening insulin for patients with type 1 diabetes. Although our study was not blinded, the differences observed between treatments were so large that they probably were not caused by the lack of blinding.

Previous studies have reported that insulin lispro (39) and aspart (39, 40) at the evening meal reduce nocturnal hypoglycemia compared with human regular insulin. Moreover, glargine, a long-acting insulin analogue (41–44), and continuous infusion of subcutaneous insulin by external minipumps (45) reduce nocturnal hypoglycemia compared with NPH insulin. However, our study is relevant to many patients who are receiving traditional formulations, such as human short-acting and NPH insulin. There is a question that our study cannot answer directly: What would occur if a short-acting insulin analogue (lispro or aspart) were used at dinner instead of human regular insulin? Although we could expect results similar to our findings on the basis of the pharmacokinetics and pharmacodynamics of NPH insulin, a trial is needed.

In conclusion, our findings indicate that patients with type 1 diabetes mellitus who receive intensive insulin therapy should split evening dosing into short-acting insulin at dinner and NPH insulin at bedtime to decrease the risk for nocturnal hypoglycemia, to decrease the level of fasting plasma glucose, and to better preserve responses to hypoglycemia.

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ARTICLE

Combination Therapy with Oral Sildenafil and Inhaled Iloprost for Severe Pulmonary Hypertension

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Background: Inhalation of the stable prostacyclin analogue iloprost is being studied for treatment of pulmonary hypertension. The selective phosphodiesterase-5 inhibitor sildenafil has been reported to cause pulmonary vasodilatation.

Objective: To evaluate the safety and effectiveness of oral sildenafil, alone and in combination with inhaled iloprost, for treatment of pulmonary hypertension.

Design: Randomized, controlled, open-label trial.

Setting: Intensive care unit.

Patients: 30 patients with severe pulmonary arterial hypertension ($n = 16$), chronic thromboembolic pulmonary hypertension ($n = 13$), or pulmonary hypertension due to aplasia of the left pulmonary artery ($n = 1$), all classified as New York Heart Association class III or IV.

Intervention: All patients received inhaled nitric oxide and aerosolized iloprost (inhaled dose, 2.8 μg). They were then randomly assigned to receive 12.5 mg of oral sildenafil, 50 mg of sildenafil, 12.5 mg of sildenafil plus inhaled iloprost, or 50 mg of sildenafil plus inhaled iloprost.

Measurements: Systemic and pulmonary arterial pressure, pulmonary arterial occlusion pressure, cardiac output, central venous pressure, peripheral arterial oxygen saturation, and arterial and mixed venous blood gases were measured during right-heart catheterization by using a Swan–Ganz catheter.

Results: In rank order of pulmonary vasodilatory potency (maximum reduction of pulmonary vascular resistance and increase in cardiac index), 50 mg of sildenafil plus iloprost was most effective, followed by 12.5 mg of sildenafil plus iloprost. Iloprost alone and 50 mg of sildenafil were almost equally effective but were less potent than the combination regimens, and the least potent treatments were 12.5 mg of sildenafil and nitric oxide. In patients who received 50 mg of sildenafil plus iloprost, the maximum change in pulmonary vasodilatory potency was −44.2% (95% CI, −49.5% to −38.8%), compared with −14.1% (CI, −19.1% to −9.2%) in response to nitric oxide. With administration of 50 mg of sildenafil plus iloprost, the area under the curve for reduction in pulmonary vasodilatory resistance surpassed that of administration of 50 mg of sildenafil alone and iloprost alone combined, the vasodilatory effect lasted longer than 3 hours, and systemic arterial pressure and arterial oxygenation were maintained. No serious adverse events occurred.

Conclusion: Although limited by the small sample and lack of long-term observations, the study shows that oral sildenafil is a potent pulmonary vasodilator that acts synergistically with inhaled iloprost to cause strong pulmonary vasodilatation in both severe pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

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Severe pulmonary hypertension is a debilitating disease with short life expectancy that often affects young people. Continuous intravenous administration of epoprostenol has been used for pulmonary vasodilatation and was shown to improve exercise capacity and survival in patients with primary pulmonary hypertension (1). However, this therapy is limited by serious infectious complications of the intravenous line, systemic side effects due to the nonselectivity of the vasodilator response, and very high costs incurred because of tachyphylaxis with long-term administration.

The vasodilatory effects of nitric oxide administered by inhalation are restricted to the pulmonary vasculature. Nitric oxide has a very short half-life and is used as a screening agent for lung vasoreactivity (2). Inhalation of aerosolized iloprost, a long-acting prostacyclin analogue, causes strong preferential pulmonary vasodilatation in both primary and secondary pulmonary hypertension (3–6). Long-term use of nebulized iloprost was shown to be beneficial in severe primary pulmonary hypertension and overt right-heart failure (7, 8), but because the drug wears off in about 60 minutes, patients must take 6 to 12 inhalations daily to achieve sustained relief of pulmonary hypertension.

Phosphodiesterases are a superfamily of enzymes that inactivate cyclic adenosine monophosphate and cyclic guanosine monophosphate, the second messengers of prostacyclin and nitric oxide. The phosphodiesterases have different tissue distributions and substrate affinities (9); in particular, phosphodiesterase-5 is abundantly ex-

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Context

Common therapies for pulmonary hypertension have disadvantages: Continuous intravenous epoprostenol may cause sepsis, hypotension, and tachyphylaxis; nitric oxide requires continuous inhalation; and inhaled iloprost requires up to 12 doses per day. Phosphodiesterase in lung tissue (PDE-5) inhibits the action of these therapies by inactivating the second messengers of prostacyclin and nitric oxide (cyclic adenosine monophosphate and cyclic guanosine monophosphate). Because sildenafil blocks the action of PDE-5, thereby causing vascular dilatation, it could be useful in treating pulmonary hypertension.

Contribution

This randomized, controlled trial of low- or high-dose sildenafil, with or without inhaled iloprost, showed dose-dependent improvement in mean pulmonary artery pressure and hemodynamics with sildenafil alone. Iloprost amplified the effects.

Implications

Sildenafil may enhance the management of pulmonary hypertension.

–The Editors

pressed in lung tissue (10). Inhibition of phosphodiesterase may augment and prolong prostanoid- and nitric oxide–related vascular effects.

The novel selective phosphodiesterase-5 inhibitor sildenafil has been approved for treatment of erectile dysfunction. Sildenafil causes only very minor systemic hemodynamic effects in healthy humans (11). Data from an experimental model of pulmonary hypertension (12) and two recent case reports (13, 14) suggested that sildenafil might be an effective pulmonary vasodilator.

We compared the pulmonary vasodilatory effect of sildenafil with that of inhaled nitric oxide and aerosolized iloprost in 30 patients with severe pulmonary hypertension. We evaluated dose–response characteristics of sildenafil alone and in combination with inhaled prostanoid during right-heart catheterization.

METHODS

Patients

Thirty patients (23 women and 7 men) with severe pulmonary hypertension (mean pulmonary arterial pressure > 40 mm Hg) were included. Sixteen patients had pulmonary arterial hypertension, as defined by the World Health Organization World Symposium on Primary Pulmonary Hypertension (15); of these patients, 10 had primary pulmonary hypertension and 6 had calcinosis, the Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia (the CREST syndrome). One patient had aplasia of the left pulmonary artery. Thirteen patients had chronic thromboembolic pulmonary hypertension and were not candidates for surgery.

All patients were admitted for testing of pulmonary vasoreactivity and evaluation of therapeutic options. Seventeen patients were tested for the first time and had not been previously treated with inhaled iloprost. Thirteen patients had been tested at least 3 months after previous vasodilator testing; 11 of these patients were receiving long-term therapy with inhaled iloprost.

Exclusion criteria were pulmonary hypertension secondary to chronic obstructive pulmonary disease, pulmonary venous congestion, congenital heart disease, acute or chronic inflammatory lung disease, pregnancy or insufficient contraceptive measures, or previous treatment with phosphodiesterase inhibitors, including theophylline preparations. The individual response to vasodilators, including inhaled nitric oxide, was neither an inclusion nor an exclusion criterion.

Treatment

The study protocol was approved by the Justus-Liebig-University Ethics Committee, and each patient gave written informed consent.

A 7.5-French Swan–Ganz fiberoptic thermodilution pulmonary artery catheter (93A-754H, Baxter Healthcare, Irvine, California) was inserted via the right jugular vein by using standard techniques. Each patient received short-term inhaled nitric oxide; the maximum vasodilator response to this agent required nitric oxide, 20 to 40 parts per million. If necessary, patients received nasal oxygen throughout the test to achieve arterial oxygen saturation greater than 88%. After hemodynamic values returned to baseline, inhaled iloprost was delivered by using an ultrasonic nebulizer (Multisonic compact [Otto Schill GmbH, Probstzella, Germany]; mass median aerodynamic diameter, 3.9 μm; duration of inhalation, 4 minutes; total inhaled dose, 2.8 μg) (16). Hemody-

Table. **Baseline Hemodynamic Data***

Group (Patients)	Heart Rate	Mean Systemic Arterial Pressure	Mean Pulmonary Arterial Pressure	Cardiac Index	Pulmonary Vascular Resistance	Arterial Oxygen Saturation	Mixed Venous Oxygen Saturation
	beats/min	*mm Hg*		*L/min per m^2*	*dyne/s per cm^{-5}*	*%*	
Sildenafil, 12.5 mg (n = 7)	73 ± 10.1	89 ± 14.6	53 ± 11.9	1.86 ± 0.8	1325 ± 728	95 ± 5.0	60 ± 12.4
Sildenafil, 50 mg (n = 8)	73 ± 16.7	100 ± 11.9	57 ± 16.4	1.95 ± 0.3	1262 ± 735	96 ± 2.0	59 ± 10.7
Sildenafil, 12.5 mg, plus iloprost (n = 7)	67 ± 6.9	93 ± 7.4	53 ± 11.6	1.86 ± 0.5	1230 ± 521	94 ± 3.7	60 ± 10.6
Sildenafil, 50 mg, plus iloprost (n = 8)	82 ± 12.4	98 ± 14.1	59 ± 11.6	1.63 ± 0.3	1471 ± 577	94 ± 3.4	51 ± 11.6

* Data are presented as the mean ± SD.

namic and gas exchange variables were measured at 5, 15, 30, 60, and 90 minutes after iloprost inhalation.

At the end of a 2-hour observation period, when hemodynamics had returned to baseline values, patients were randomly assigned to one of four treatment groups: 12.5 mg of oral sildenafil alone ($n = 7$); 12.5 mg of oral sildenafil, followed by 2.8 μg of inhaled iloprost 1 hour later ($n = 7$); 50 mg of oral sildenafil alone ($n = 8$); or 50 mg of oral sildenafil, followed by 2.8 μg of inhaled iloprost 1 hour later ($n = 8$). Patients were assigned to the therapeutic regimens by using computerized randomization in groups of four; no more than two patients in a row were assigned to one group.

Hemodynamic measurements and blood sampling were performed at 15, 30, 60, 90, and 120 minutes (and at 150 and 180 minutes in the group receiving 12.5 mg of sildenafil plus iloprost and in the group receiving 50 mg of sildenafil plus iloprost) after administration of oral sildenafil. To assess the overall vasodilator response, the area under the curve (AUC) of reduction in pulmonary vascular resistance was calculated as the integral of the difference between preintervention baseline values until pulmonary vascular resistance again reached 95% of baseline values or 120 minutes.

Statistical Analysis

Data are given as the mean and 95% CIs. For every variable, the response to vasodilator treatment was considered significant if the 95% ($P < 0.05$), 99% ($P < 0.01$), or 99.9% ($P < 0.001$) CI of the difference between pretreatment and post-treatment values did not overlap with zero. Two-way analysis of variance (ANOVA) was performed to test for significant differences and possible interaction of vasoreactivity to different vasodilators with underlying disease. One-way ANOVA with the Scheffé post-test was used to determine hemodynamic responsiveness to the vasodilator regimens when two-way ANOVA indicated that underlying disease was a significant factor.

RESULTS

Baseline Hemodynamics

The Table shows baseline hemodynamics in all treatment groups. All patients had severe pulmonary hypertension and low cardiac index values. No pulmonary venous congestion was observed, as indicated by low pulmonary arterial occlusion pressure (8.7 ± 0.6 mm Hg). On ANOVA, the groups did not differ significantly in any baseline characteristic.

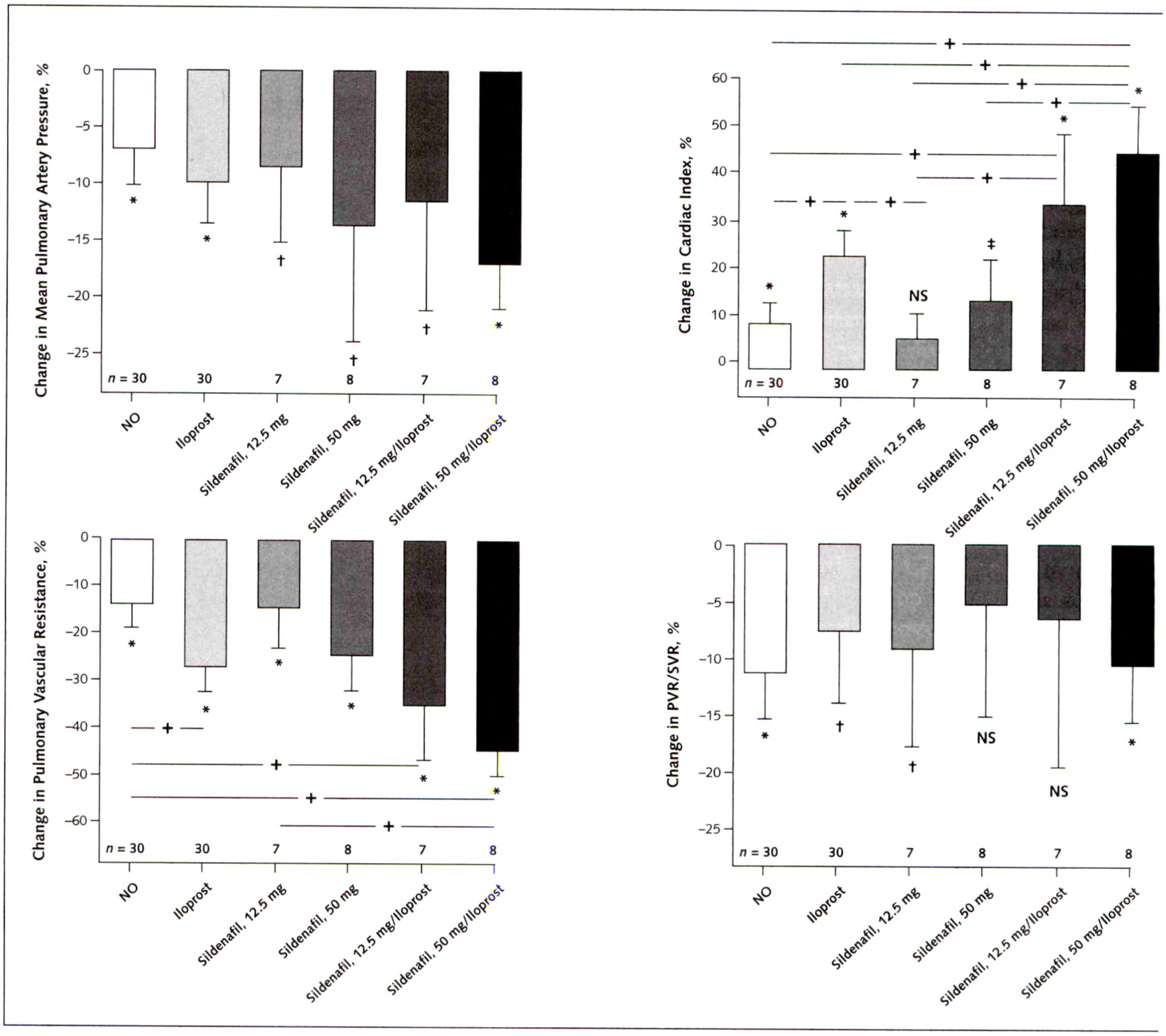
Inhaled Nitric Oxide

Inhalation of nitric oxide decreased mean pulmonary arterial pressure (change, −7.0% [95% CI, −3.8% to 10.2%]), increased the cardiac index (change, 7.9% [CI, 3.4% to 12.5%]), and decreased pulmonary vascular resistance (change, −14.1% [CI, −19.1% to −9.2%]) (**Figure 1**). The pulmonary selectivity of the vasodilatory effect was indicated by a significant reduction in the ratio of pulmonary to systemic vascular resistance. The decrease in pulmonary vascular resistance in response to inhaled nitric oxide did not differ significantly among groups (**Figure 2**). The effects of nitric oxide wore off within 15 minutes.

Inhaled Iloprost

Aerosolized iloprost decreased the pulmonary vascular resistance by 27.1% (CI, 22.2% to 32.1%) and increased the cardiac index by 22.8% (CI, 17.6% to

Figure 1. **Hemodynamic responses to vasodilators.**



Bars show the maximum changes from preintervention baseline values; error bars represent CIs. Analysis of variance with the Scheffé post-test for intergroup comparison indicated significant differences ($P < 0.001$); plus signs bracketed by horizontal bars show these relationships. NO = nitric oxide; NS = not significant; PVR/SVR = ratio of pulmonary vascular resistance to systemic vascular resistance. *$P < 0.001$, †$P < 0.05$, ‡$P < 0.01$ for differences between pretreatment and post-treatment values.

27.9%) (**Figure 1**). The decrease in the ratio of pulmonary to systemic vascular resistance indicated preferential pulmonary vasodilatation. No significant differences among groups in the vasodilator response to inhaled iloprost were observed (**Figure 2**). The effects of iloprost wore off within 60 to 90 minutes.

Oral Sildenafil

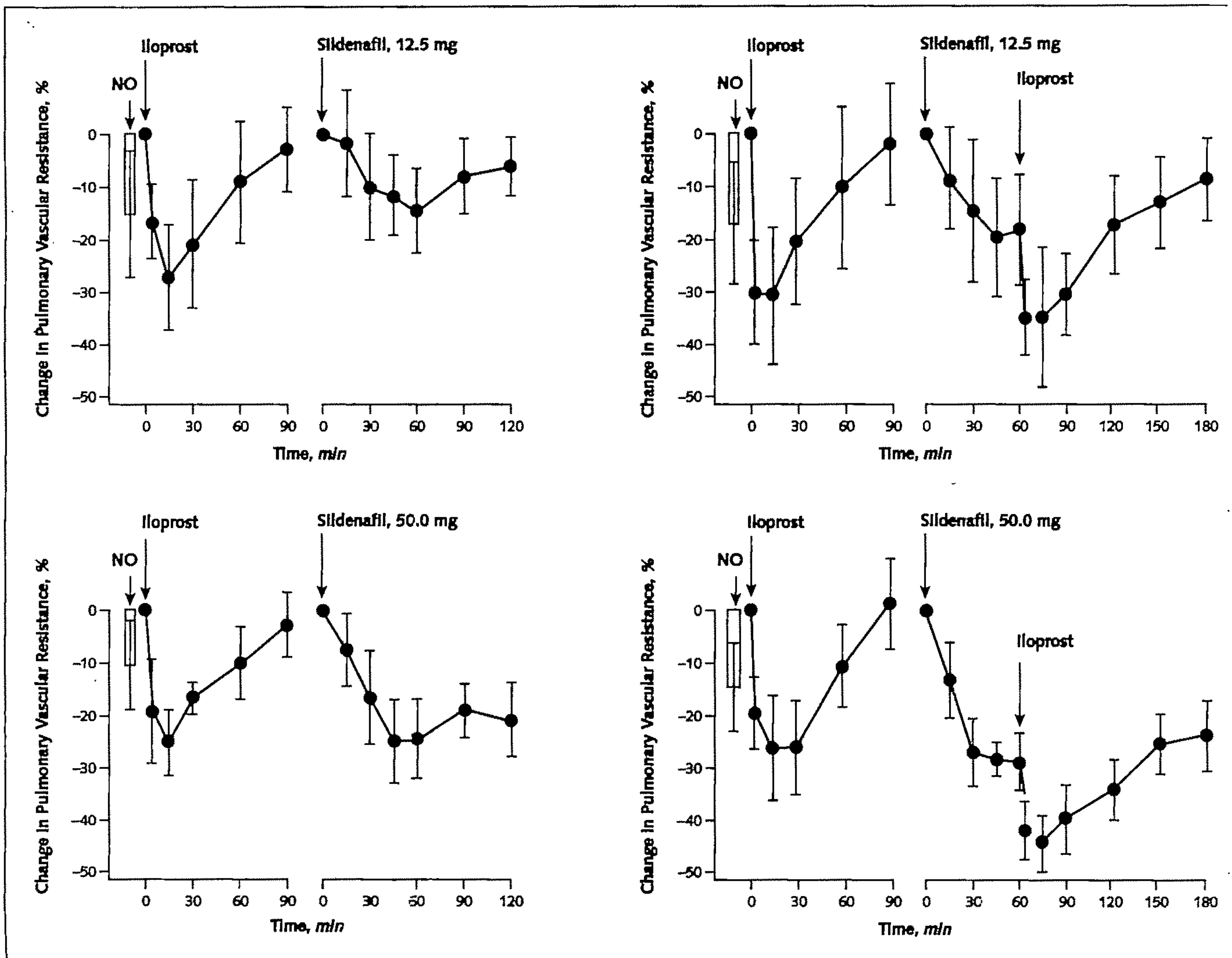
Administration of 12.5 mg or 50 mg of sildenafil decreased mean pulmonary arterial pressure in a dose-dependent manner (change, −8.5% [CI, −15.1% to −1.9%] and −13.5% [CI, −23.8% to −3.2%], respectively) (**Figure 1**). The cardiac index increased by 5.0%

(CI, −0.5% to 10.5%) and 13.2% (CI, 4.3% to 22.2%), and pulmonary vascular resistance decreased by 14.7% (CI, 6.6% to 22.7%) and 24.3% (CI, 16.7% to 31.8%). The decrease in the ratio of pulmonary to systemic vascular resistance indicated preferential pulmonary vasodilatation. Arterial oxygen did not decrease significantly (data not shown), and no adverse events were observed. The vasodilatory response to sildenafil began within 15 minutes of administration and reached a plateau after 45 to 60 minutes; the 50-mg dose of sildenafil was still effective after 120 minutes (Figure 2).

Combination Therapy

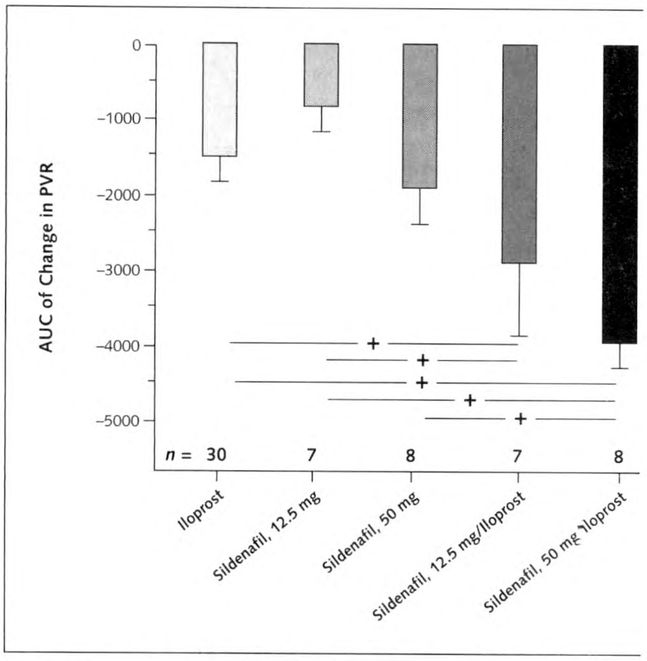
Inhalation of iloprost 1 hour after oral intake of 12.5 mg or 50 mg of sildenafil significantly increased the pulmonary vasodilator response compared with each single intervention (Figures 1 and 2). It also decreased pulmonary vascular resistance ($P < 0.001$, ANOVA) and increased cardiac index ($P < 0.001$, ANOVA) to a significantly greater extent than did the single interventions and maintained good pulmonary vasodilatation. The maximum reduction in pulmonary vascular resistance was most pronounced in patients who received 50

Figure 2. **Time to decrease in pulmonary vascular resistance in response to vasodilator challenge.**



Data are presented as the mean; error bars indicate CIs. Arrows indicate administration of therapy. The bars at the left of each panel show the maximum reduction in pulmonary vascular resistance caused by initial nitric oxide (*NO*) inhalation. Pretreatment baseline values are set at 100%.

Figure 3. **Area under the curve (*AUC*) of reduction in pulmonary vascular resistance (*PVR*) in response to therapy.**



To assess mean AUCs and CIs (indicated by the error bars), we calculated the integral of difference between preintervention baseline values until pulmonary vascular resistance again reached 95% of baseline values or 120 minutes had passed. Analysis of variance with the Scheffé post-test for intergroup comparison indicated significant differences ($P < 0.001$); plus signs bracketed by horizontal bars demonstrate these relationships.

mg of sildenafil plus iloprost (change, −44.2% [CI, −49.55% to −38.8%]). The overall vasodilatory response to the combined interventions lasted beyond the 180-minute observation period. The AUC for reduction in pulmonary vascular resistance after combination therapy was greater than the sum of the AUCs for each single intervention, at either dose of sildenafil plus iloprost ($P < 0.001$, ANOVA) (**Figure 3**). No significant decrease in arterial oxygen saturation (data not shown) and no adverse events occurred during combination therapy.

Subgroup Analysis

Baseline hemodynamic values did not significantly differ between patients with primary pulmonary hypertension and those with chronic thromboembolic pulmonary hypertension. On two-way ANOVA to assess the effect of diagnosis on hemodynamic responsiveness to monotherapy and combination therapy, no significant difference could be detected on the basis of diagnosis. Furthermore, no interaction was seen when patients with primary pulmonary hypertension were compared with all other patients and with those who had chronic thromboembolic pulmonary hypertension.

DISCUSSION

Lung tissue is a rich source of phosphodiesterases. Phosphodiesterase-3 and phosphodiesterase-4 by hydrolyzation assist in degradation of cyclic adenosine monophosphate, and phosphodiesterase-5 assists in decay of cyclic guanosine monophosphate. The actions of these phosphodiesterases limit the vasodilatory effects of adenylate cyclase stimuli (such as prostanoids) and guanylate cyclase stimuli (such as nitric oxide) (17). Cross-talk between the cyclic adenosine monophosphate and the cyclic guanosine monophosphate pathways has been demonstrated; inhibition of phosphodiesterase-3 by cyclic guanosine monophosphate is the most prominent example (9). Moreover, phosphodiesterases may be up-regulated in response to increased second messenger levels as a negative feedback loop (9).

We found that the phosphodiesterase-5–selective inhibitor sildenafil caused strong dose-dependent pulmonary vasodilatation, even in the absence of exogenous nitric oxide administration, in patients with pulmonary arterial hypertension (many of whom had primary pulmonary hypertension) and those with chronic thromboembolic pulmonary hypertension. Only 3 of 30 patients were considered responsive to nitric oxide, on the basis of reduction of pulmonary arterial pressure by more than 20% and a decrease in pulmonary vascular resistance of more than 20% (18). However, in accordance with our findings and those of other investigators (5, 7), inhaled iloprost provoked substantially stronger pulmonary vasorelaxation in most of these patients. This was also true for the subgroup of patients with chronic thromboembolic pulmonary hypertension, in whom marked lung vasodilatation was observed in response to aerosolized prostanoid (7). Most surprising, as seen in an experimental model of pulmonary hypertension (12), the maximum vasodilatory response to sildenafil markedly surpassed that provoked by nitric oxide in the same patients, and the decrease in the ratio of pulmonary to systemic vascular resistance indicated preferential pulmonary vasodilatation despite oral administration of the phosphodiesterase inhibitor. Thus, substantial baseline stimulation of guanylate cyclase in the lung vasculature of patients with hypertension may be assumed and is only partly attributable to nitric oxide; thus, strong pulmonary vasodilatation results when phosphodiesterases block the breakdown of the second messenger, cyclic guanosine monophosphate.

Administration of oral sildenafil plus inhaled iloprost produced a much greater vasodilatory response than did each single agent. The AUC of the reduction in pulmonary vascular resistance with 12.5 mg or 50 mg of sildenafil plus iloprost exceeded the summed AUCs from patients receiving sildenafil alone at either dose or iloprost alone. The decrease in the ratio of pulmonary to systemic vascular resistance in the combination-therapy groups again indicated preferential pulmonary vasodilatation over systemic vasodilatation, and arterial oxygenation did not worsen. Of note, the maximum decrease in pulmonary vascular resistance in patients with chronic pulmonary hypertension approached nearly 50% in response to 50 mg of sildenafil plus iloprost, although this group did not include classic responders to vasodilator treatment, as indicated by the moderate effect of nitric oxide inhalation. The extent to which a cyclic guanosine monophosphate–linked inhibition of phosphodiesterase-3 and, thus, prolongation of prostanoid-induced cyclic adenosine monophosphate contribute to this synergism, and whether additional mechanisms are at work, are yet to be elucidated.

Our study had limitations. Because our sample was small and long-term observations are lacking, our current data are too preliminary to allow recommendations for new therapeutic strategies. Furthermore, no definitive conclusion about the influence of etiology of the disease or differences in baseline characteristics can be made at this stage. Further controlled studies in larger samples are needed to address these issues.

We conclude that oral sildenafil is an effective pulmonary vasodilator in both pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. In combination with inhaled iloprost, this treatment has synergistic hemodynamic effects with no loss of selectivity for the pulmonary vasculature. Combined administration of oral sildenafil and inhaled iloprost may become a novel approach to achieve pulmonary vasodilatation and long-term antiremodeling in pulmonary hypertension of various causes.

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BRIEF COMMUNICATION

Change in Coronary Flow Reserve on Transthoracic Doppler Echocardiography after a Single High-Fat Meal in Young Healthy Men

Takeshi Hozumi, MD; Marc Eisenberg, MD; Kenichi Sugioka, MD; Aravind R. Kokkirala, MD; Hiroyuki Watanabe, MD; Masakazu Teragaki, MD; Junichi Yoshikawa, MD; and Shunichi Homma, MD

Background: **High-fat meals and elevated triglyceride levels are associated with cardiovascular disease. In recent studies of brachial artery vasoactivity, a single high-fat meal reduced endothelial function in young healthy men. It is unknown whether coronary microcirculation is affected after high-fat meals.**

Objective: **To evaluate change in coronary flow reserve after a single high-fat meal.**

Design: **Controlled interventional study.**

Setting: **University hospitals.**

Patients: **15 young healthy men (mean age [±SD], 29 ± 4 years).**

Intervention: **Coronary flow reserve was determined by using transthoracic Doppler echocardiography before and after consumption of a high-fat meal in all 15 men and before and after consumption of a low-fat meal in 5 of 15 men.**

Measurements: **Coronary flow reserve, lipid levels, and hemodynamic characteristics.**

Results: **In all men, triglyceride levels increased significantly from baseline 5 hours after the high-fat meal, from 1.1 mmol/L to 2.8 mmol/L (100 mg/dL to 250 mg/dL) ($P < 0.001$). Average coronary flow reserve was 4.02 before and 3.30 5 hours after the high-fat meal (decrease, 18% [95% CI, 13% to 23%]). In the 5 men who received both meals, mean coronary flow reserve decreased by 0.79 after the high-fat meal and increased by 0.07 after the low-fat meal (difference, −0.86 [CI, −1.36 to −0.37]; $P = 0.03$). Mean triglyceride levels increased by 1.6 mmol/L (140 mg/dL) after the high-fat meal and 0.1 mmol/L (10 mg/dL) after the low-fat meal (difference, 1.5 mmol/L [CI, 0.3 to 2.7 mmol/L], 130 mg/dL [CI, 23 to 236 mg/dL]; $P = 0.03$).**

Conclusions: **Coronary flow reserve decreased after a single high-fat meal in young healthy men. High-fat meals may be detrimental to coronary microcirculation.**

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High-fat meals and elevated triglyceride levels are associated with cardiovascular diseases (1–3). In recent studies analyzing brachial artery vasoactivity, a single high-fat meal reduced endothelial function in young healthy men without coronary risk factors (4–6). High-fat meals may have an unfavorable effect on coronary microcirculation as well as peripheral vasoactivity. To our knowledge, however, no report has evaluated the effect of high-fat meals on coronary microcirculation in humans.

Transthoracic Doppler echocardiography with a high-frequency transducer provides noninvasive estimations of coronary flow reserve, which is defined as the ratio of coronary flow during peak flow response induced by dilatation of coronary microvessels to resting coronary flow (7, 8). We used Doppler echocardiography to evaluate change in coronary flow reserve, which indicates a change in coronary microcirculation, in young healthy men after a single high-fat meal.

METHODS

Study Group

We studied 15 young healthy men (mean age [±SD], 29 ± 4 years) who had no evidence of coronary artery disease. Women were not included because we wanted to exclude the effect of estrogen on coronary circulation. None of the men had a history of hypertension, diabetes mellitus, hypercholesterolemia, or tobacco abuse, all of which may affect coronary circulation. Mean body mass index (±SD) was 24.6 ± 3.6 kg/m^2.

Study Protocol

Studies were started after a 12-hour overnight fast. We obtained written informed consent from all of the men, and the Institutional Review Boards of Columbia University and Osaka City University Medical School approved the protocol. Fasting blood samples were drawn to determine levels of serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Coronary flow reserve was then assessed by using transthoracic Doppler echocardiography. All 15 men consumed liquid high-fat meals (1200 calories, 100 g fat, 50 g saturated fat, 300 mg cholesterol, 47 g carbohydrates, 27 g total protein). Five of the 15 men were then randomly selected to consume a liquid low-fat meal (1200 calories, 10 g fat, 2 g

Context

Some studies show that acute elevations in plasma triglyceride levels after a high-fat meal alter vascular tone and impair endothelial function.

Whether a high-fat meal and associated hypertriglyceridemia affect coronary microcirculation in healthy people without known cardiovascular disease is unclear.

Contribution

Five hours after a single high-fat meal, triglyceride levels in 15 healthy young men increased from 1.1 mmol/L to 2.8 mmol/L (100 mg/dL to 250 mg/dL) and coronary flow reserve decreased by 18% (95% CI, 13% to 23%).

Implications

A single high-fat meal can adversely affect coronary microcirculation in young healthy men.

—The Editors

saturated fat, 6 mg cholesterol, 273 g carbohydrates, 30 g total protein) within 1 week of consumption of the high-fat meal. The composition of high-fat meals and low-fat meals remained consistent during the study period. Coronary flow reserve was measured again 5 hours after consumption of high-fat and low-fat meals; this interval was chosen on the basis of previous reports demonstrating the time course of blood triglyceride levels and endothelial dysfunction after high-fat meals (9). Lipid levels were also determined 5 hours after the high-fat meals.

Coronary Flow Reserve Measurement by Transthoracic Doppler Echocardiography

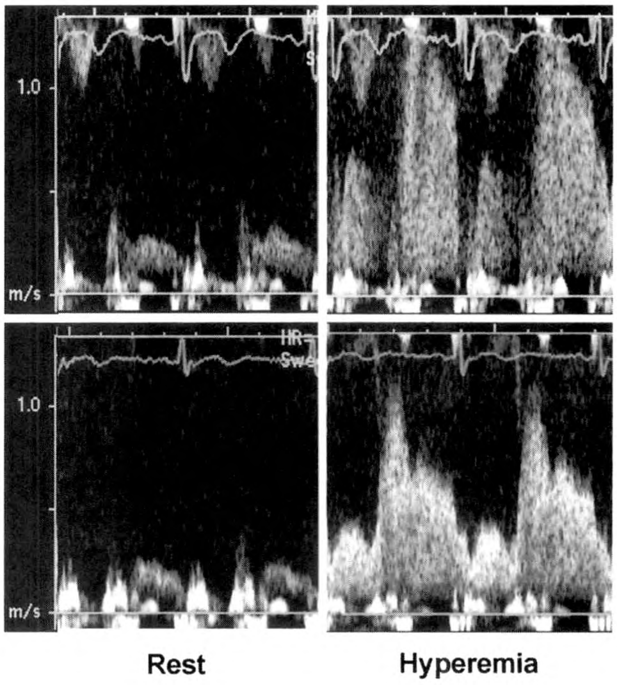
The SONOS 5500 digital ultrasonography system (Agilent Technologies, Andover, Massachusetts) or the Sequoia digital ultrasonography system (Acuson, Mountain View, California) was used to assess coronary flow reserve, as described elsewhere (7, 8). Both systems had high-frequency transducers (5 to 8 MHz and 5 to 7.5 MHz, respectively). For color Doppler flow mapping, velocity range was set at 9.6 to 16.0 cm/s in the Agilent system and 8.6 to 11.0 cm/s in the Acuson system. The color gain was adjusted to provide optimal images. Briefly, acoustic window was found in the midclavicular line in the fourth or fifth intercostal space in the left lateral decubitus position. The left ventricle was imaged in the long-axis cross-section, and the ultrasound beam was then inclined laterally. Next, coronary blood flow in the left anterior descending coronary artery (middle to distal) was searched by using color Doppler flow mapping. After a sample volume (1.5 mm wide) was positioned on the color signal in the left anterior descending coronary artery, fast Fourier transformation analysis recorded Doppler spectral velocity tracings of coronary flow velocity. Angles were corrected because of incident Doppler angle (mean angle [±SD], 45 degrees ± 5 degrees), although we tried to make the ultrasound beam as parallel as possible to the flow of the left anterior descending coronary artery. All studies were continuously recorded on 0.5-inch S-VHS videotapes for off-line analysis. The ultrasonography technicians were unaware of patients' meal status.

We first recorded baseline spectral Doppler signal in the left anterior descending coronary artery. Adenosine or adenosine triphosphate was intravenously administered (0.14 mg/kg of body weight per minute) for 2 minutes to record spectral Doppler signals. This allowed us to obtain peak flow response induced by dilatation of coronary microvessels. All patients had continuous heart rate and electrocardiographic monitoring. Systolic and diastolic blood pressure were recorded at baseline, at peak flow response, and at recovery. An experienced investigator who was blinded to the order of preprandial and postprandial data used the ultrasonography system computer to obtain measurements off-line by tracing the contour of the spectral Doppler signal. Mean diastolic velocity was measured at baseline and at peak flow response. An average of the measurements was obtained in three cardiac cycles. Coronary flow reserve was defined as the ratio of mean diastolic velocity at peak flow response to basal mean diastolic velocity.

Statistical Analysis

A paired, two-tailed Student *t*-test was used to evaluate the differences between preprandial and postprandial states and the differences between baseline and hyperemic data before and after the high-fat meal. The primary null hypothesis was that the change in coronary flow reserve after a high-fat meal would not differ from that after a low-fat meal. Secondary null hypotheses were that the change in triglyceride levels after a high-fat meal would not differ from the change in coronary flow

Figure 1. **Spectral Doppler recording in the left anterior descending coronary artery before (*top*) and after (*bottom*) a high-fat meal.**



HR = heart rate.

reserve after a low-fat meal and that the change in coronary flow reserve after a high-fat meal would not correlate with the change in triglyceride levels after a high-fat meal. Analysis of the changes in coronary flow reserve and triglyceride levels after high-fat and low-fat meals was performed by paired *t*-test of the differences between preprandial and postprandial values. A sign test was used to obtain the *P* value for comparisons between the changes in coronary flow reserve and in triglyceride levels after high- and low-fat meals. The association between the change in coronary flow reserve and the change in triglyceride levels after the high-fat meal was assessed by using the Pearson correlation. Analyses were performed by using SAS, version 7.00 (SAS Institute, Inc., Cary, North Carolina).

To evaluate reproducibility of coronary flow reserve measurement, coronary flow reserve was assessed by transthoracic Doppler echocardiography twice in seven randomly selected participants before the high-fat meal. The two measurements were obtained more than 10 minutes apart. Reproducibility was calculated as the standard deviation of the differences between the first and second measurement of coronary flow reserve and was expressed as a percentage of the average value. Average reproducibility for measurement of coronary flow reserve was 5.3%.

Role of the Funding Source

The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

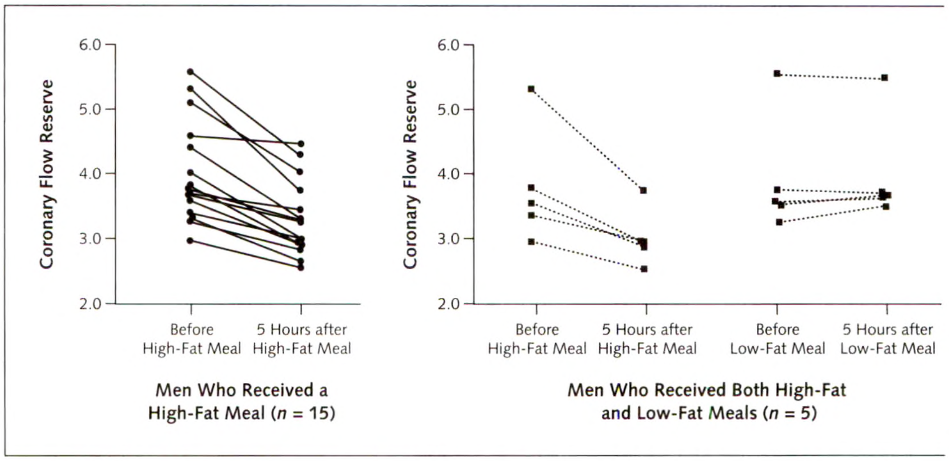
In all 15 men, triglyceride levels increased significantly from baseline after the high-fat meal, from 1.1 to 2.8 mmol/L (100 mg/dL to 250 mg/dL) ($P < 0.001$). No statistically significant changes in total cholesterol level were observed (4.5 mmol/L vs. 4.4 mmol/L [174 mg/dL vs. 171 mg/dL]), and no difference was observed in mean diastolic coronary velocity at rest before and after the high-fat meal (24.3 cm/s vs. 25.4 cm/s). Coronary flow velocity at peak flow response was lower than the value obtained before consumption of the high-fat meal (81.3 cm/s vs. 94.0 cm/s; $P < 0.001$). As a result, average coronary flow reserve changed from 4.02 before the high-fat meal to 3.30 5 hours after it (decrease, 18% [95% CI, 13% to 23%]) (**Figures 1** and **2**). No statistically significant change in heart rate or systolic and diastolic blood pressure occurred after the high-fat meal.

The **Table** shows data from the 5 men who received both high-fat and low-fat meals. Coronary flow reserve decreased by a mean of 0.79 after the high-fat meal and increased by a mean of 0.07 after the low-fat meal (difference, −0.86 [CI, −1.36 to −0.37]; $P = 0.03$) (**Figure 2**). The mean increase in triglyceride levels was 1.6 mmol/L (140 mg/dL) after the high-fat meal and 0.1 mmol/L (10 mg/dL) after the low-fat meal (difference, 1.5 mmol/L [CI, 0.3 to 2.7 mmol/L], 130 mg/dL [CI, 23 to 236 mg/dL]; $P = 0.03$). However, in all participants, the change in coronary flow reserve after the high-fat meal did not correlate significantly with the change in triglyceride levels ($r = 0.01$; $P > 0.2$).

DISCUSSION

Recent studies analyzing brachial artery vasoactivity showed that a single high-fat meal reduced endothelial

Figure 2. **Coronary flow reserve in 15 men who received a high-fat meal (*left*) and in 5 men who received both high- and low-fat meals (*right*).**



The 5 men in the right-hand graph are a subset of the 15 men in the left-hand graph.

function in young healthy men who had no coronary risk factors (4–6). Vogel and colleagues (4) examined flow-mediated brachial artery reactivity after high-fat meals and low-fat meals by using high-resolution ultrasonography. Flow-mediated vasodilation decreased after the high-fat meal, while flow-mediated dilatation did not change significantly after the low-fat meal. The authors suggested that hypertriglyceridemia induced by high-fat meals, not low-fat meals, affected flow-mediated vasoactivity. Plotnick and associates (5) also found no significant change in flow-mediated dilatation after a high-fat meal and pretreatment with vitamin C and E, suggesting that antioxidants may suppress possible effects of hypertriglyceridemia on endothelial function. Lundman and coworkers (6) investigated both endothelium-dependent and endothelium-independent brachial dilatation during transient hypertriglyceridemia induced by infusion of a hypertriglyceridemia emulsion. Both endothelium-dependent and endothelium-independent vasodilation significantly decreased after transient hypertriglyceridemia, suggesting that high-fat meals may have an unfavorable effect on coronary microcirculation.

Coronary flow reserve, which reflects coronary microcirculation (10–14), has been estimated by measuring coronary flow velocity using a Doppler guide wire or catheter in catheterization laboratories (15–17). Although these techniques are already established and accurate, we did not consider them suitable for evaluating coronary flow reserve in our participants. Transthoracic Doppler echocardiography with a high-frequency transducer enabled us to evaluate coronary flow reserve before and 5 hours after a high-fat meal. In a recent report (7), we demonstrated that noninvasive measurement of coronary flow velocities and coronary flow reserve by transthoracic Doppler echocardiography accurately reflects invasive Doppler guide-wire measurements. We also showed, in the same report, that observer variability in measurement of coronary flow velocity was low, and our current study shows that these measurements are highly reproducible.

In our current study, resting coronary flow velocity was very similar before and after the high-fat meal, and resting velocity and peak flow velocity were relatively unchanged after the low-fat meal. The difference in change in coronary flow reserve after the high-fat and low-fat meals seems to be mainly due to change in coronary flow velocity at peak flow response during the high-fat meal. Our findings suggest that coronary microcirculation at peak flow response was affected after the high-fat meal, which caused transient hypertriglyceridemia. This may have led to reduction in coronary flow reserve after the high-fat meal. However, coronary microcirculation, both at rest and during peak flow response, was not affected after the low-fat meal, which did not induce transient hypertriglyceridemia. Thus, after the low-fat meal, coronary flow reserve did not change significantly.

Our study does not clarify the precise mechanism by which high-fat meals reduce coronary flow reserve. However, our results may correspond to other reports indicating that the effect of high-fat meals on brachial vasoactivity reflects endothelial function (4–6). Pretreatment with antioxidants has blocked reduction in endothelial function, suggesting an oxidative stress mechanism (5). Similar mechanisms may contribute to reduced coronary flow reserve after high-fat meals. In our study, however, change in triglyceride levels did not correlate with change in coronary flow reserve. This may be due to the small sample size and to the fact that other lipids may have affected coronary flow reserve. Further investigation may be necessary to clarify the mechanism associated with reduced coronary flow reserve after high-fat meals.

Previous studies reported that high-fat meals and elevated triglyceride levels are associated with cardiovascular diseases (1–3). Endothelial dysfunction, which precedes atherosclerosis, has been seen after hypertriglyceridemia in healthy volunteers (4–6). In our study, coronary flow reserve decreased after a single high-fat meal in healthy young men, suggesting impaired coronary microcirculation. Although we did not include men with coronary risk factors, it is possible that reduction in coronary flow reserve after a high-fat meal contributes to the syndrome of postprandial angina.

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Table. **Change in Lipid Levels, Coronary Flow Data, and Hemodynamic Characteristics in 5 Men after High- and Low-Fat Meals***

Variable	High-Fat Meal		Change	Low-Fat Meal		Change
	Before	5 Hours after		Before	5 Hours after	
Lipid levels, *mmol/L (mg/dL)*						
Mean triglyceride level	1.4 (121)	3.0 (261)		1.6 (139)	1.7 (150)	
Mean total cholesterol level	4.4 (171)	4.3 (167)		4.7 (181)	4.5 (176)	
Mean HDL cholesterol level	1.0 (41)	0.9 (37)		1.1 (43)	1.0 (39)	
Mean LDL cholesterol level	2.7 (104)	2.2 (85)		2.9 (112)	3.0 (117)	
Coronary flow data						
Mean diastolic velocity, *cm/s*						
Baseline	26.7	28.8		26.3	26.6	
Hyperemia	98.0	84.8		98.3	101.7	
Coronary flow reserve						
Case 1	2.96	2.54	−0.42	3.20	3.42	0.22
Case 2	3.79	2.93	−0.86	3.69	3.65	−0.04
Case 3	3.56	2.88	−0.68	3.46	3.61	0.15
Case 4	3.39	2.98	−0.41	3.51	3.59	0.08
Case 5	5.31	3.72	−1.59	5.46	5.40	−0.06
Mean	3.80	3.01	−0.79	3.86	3.93	0.07
Hemodynamic characteristic						
Mean heart rate, *beats/min*						
Baseline	64	65		66	68	
Hyperemia	70	70		77	77	
Mean systolic blood pressure, *mm Hg*						
Baseline	110	107		108	109	
Hyperemia	104	108		104	104	
Mean diastolic blood pressure, *mm Hg*						
Baseline	76	66		67	73	
Hyperemia	73	71		68	68	

* HDL = high-density lipoprotein; LDL = low-density lipoprotein.

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Is C-Reactive Protein Specific for Vascular Disease in Women?

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Background: **C-reactive protein (CRP) predicts risk for future cardiovascular events in asymptomatic individuals. However, because CRP also predicts total mortality, its specificity for vascular disease is uncertain.**

Objective: **To compare the predictive value of CRP for cancer and cardiovascular disease, the major determinants of mortality.**

Design: **Prospective, nested case–control study.**

Setting: **The Women's Health Study, an ongoing prospective cohort study involving 28 345 U.S. women 45 years of age and older who were healthy at the time of enrollment.**

Participants: **643 women who subsequently developed cancer or had cardiovascular events; 643 age- and smoking-matched women who remained free of either disease during 58-month follow-up.**

Measurements: **Baseline CRP levels.**

Results: **Little evidence showed that increasing quartiles of baseline CRP predicted incident cancer (adjusted relative risks, 1.0, 1.2, 1.1, and 1.3; *P* for trend > 0.2). In contrast, increasing quartiles of baseline CRP were a strong marker of risk for future cardiovascular disease (adjusted relative risks, 1.0, 2.9, 3.4, and 5.6; *P* for trend < 0.001).**

Conclusion: **C-reactive protein appears to independently predict cardiovascular events but not cancer.**

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See editorial comment on pp 550-552.

Recent evidence suggests that atherosclerosis is in part a chronic low-grade inflammatory condition (1), and prospective epidemiologic studies have demonstrated that plasma markers of inflammation, such as C-reactive protein (CRP), are strong independent predictors of future coronary events in apparently healthy persons (2–6). However, as an acute-phase reactant, CRP increases dramatically in various pathologic conditions. Moreover, CRP has been shown to predict all-cause mortality (7, 8), an observation that raises the possibility that CRP may not be specific for vascular disease. To evaluate this hypothesis, we directly compared the predictive value of CRP for incident cancer and cardiovascular disease, the two most important determinants of all-cause mortality in the western world.

METHODS

We performed a prospective, nested case–control analysis within the Women's Health Study, an ongoing randomized, double-blind, placebo-controlled trial of aspirin and vitamin E for primary prevention of heart disease and cancer, which involves 39 876 U.S. women 45 years of age and older. Of these study participants, 28 345 (71%) provided baseline blood samples, which were stored at −70 °C until the time of laboratory analysis. In the Women's Health Study, all participants are followed prospectively for incident health events, including cancer and cardiovascular events. The methods used for cohort follow-up, end-point ascertainment, and adjudication for both cancer and cardiovascular events are described in detail elsewhere (5, 9).

For this study, we defined case-patients as apparently healthy women who provided an adequate baseline plasma sample and who subsequently developed cancer ($n = 513$) or an acute cardiovascular event (myocardial infarction, stroke, or cardiovascular death) ($n = 130$) over a mean follow-up period of 58 months. For each woman who had confirmed cancer or cardiovascular event during follow-up, one control of the same age (± 1 year) and smoking habit (former smoker, current smoker, or nonsmoker) was selected from among participants who provided baseline plasma samples and remained free of reported disease during the same follow-up period. Using these criteria, we evaluated 643 case-patients and an equal number of controls in two separate matched pairs, one for cancer ($n = 513$) and another for cardiovascular events ($n = 130$). The Institutional Review Board of the Brigham and Women's Hospital approved this study.

For each case-patient and control, plasma stored since the baseline examination was thawed and assayed for CRP levels by using a high-sensitivity assay (Dade Behring, Newark, Delaware) (10). Blood specimens

Context

Inflammatory markers, such as C-reactive protein (CRP), independently predict future coronary artery disease in patients without known disease at baseline.

However, an elevated CRP level also predicts all-cause mortality; therefore, it may not be specific for cardiovascular disease.

Contribution

This prospective case–control study showed that CRP level predicted the development of acute cardiovascular events but not cancer among 28 345 women followed for a mean of 58 months.

Clinical Implications

In women, CRP level appears specifically predictive of cardiovascular disease but not cancer.

This study adds further evidence that CRP levels may be useful in the clinical prediction of cardiovascular risk, at least in populations.

—The Editors

were analyzed in blinded pairs with the position of the patient's specimen varied at random to reduce the possibility of systematic bias and to decrease interassay variability. The day-to-day precision values, at CRP concentrations of 0.15 mg/L and 0.49 mg/L, were 4.9% and 6.4%, respectively.

Because CRP values are skewed rightward, median plasma concentrations were computed, and the significance of any difference in the distributions between the case-patients and controls was assessed by performing the Wilcoxon rank-sum test. We then used conditional logistic regression models to determine the risk for developing cancer or cardiovascular end points after dividing the study sample into quartiles on the basis of the distribution of the control group. Adjusted estimates of risk were obtained by use of similar models that accounted for the matching variables and that controlled for randomized treatment assignment (for vitamin E, aspirin, or both), body mass index, diabetes mellitus, history of hyperlipidemia, history of hypertension, and parental history of coronary heart disease.

All analyses were performed by using SAS software, release 8.2 (SAS Institute, Inc., Cary, North Carolina). All *P* values were two tailed, and CIs were computed at the 95% level.

The funding sources played no role in the design, conduct, or reporting of the study.

RESULTS

Table 1 shows the baseline characteristics of the study participants. We noted no significant differences at baseline between women who subsequently developed cancer and those who did not. As expected, women who

Table 1. **Baseline Clinical Characteristics of the Study Participants**

Characteristic	Incident Cancer		Incident Cardiovascular Events	
	Case-Patients (n = 513)	Controls (n = 513)	Case-Patients (n = 130)	Controls (n = 130)
Mean age, y*	56.7	56.7	60.4	60.3
Mean body mass index, *kg/m²*	25.9	25.8	27.6	25.7
Hyperlipidemia, %	30.6	29.6	46.9	28.5
History of hypertension, %	27.3	25.0	56.9	34.9
History of diabetes mellitus, %	2.9	2.5	10.8	3.1
Parental history of myocardial infarction before age 60 y, %	12.4	14.9	22.7	10.7
Smoking status, %*				
Current smoker	15.2	15.2	26.9	26.9
Past smoker	39.4	39.4	31.5	31.5
Never smoker	45.4	45.4	41.5	41.5
Current use of hormone replacement therapy, %	42.9	47.4	44.6	40.0
Frequency of vigorous exercise, %				
Rarely or never	37.6	39.0	46.9	43.1
<1 time/wk	18.1	17.7	20.8	27.7
1–3 times/wk	34.3	30.2	25.4	21.5
>3 times/wk	9.9	13.1	6.9	7.7
Median C-reactive protein level, *mg/L*	2.6	2.5	5.1	2.8

* Case-patients and controls are matched for age and smoking status.

Table 2. **Relative Risk for Future Cancer and Cardiovascular Events, according to Baseline Plasma C-Reactive Protein Level***

Variable	Quartiles of Baseline C-Reactive Protein Level				*P* Value for Trend
	1st (<1.0 mg/L)	2nd (1.0–2.4 mg/L)	3rd (2.5–5.6 mg/L)	4th (≥5.7 mg/L)	
Distribution of participants, *n* (%)					
Controls	164 (25.6)	159 (24.8)	160 (24.9)	159 (24.8)	
Incident cancer	123 (24.0)	131 (25.5)	116 (22.6)	143 (27.9)	
Incident CVD	7 (5.4)	25 (19.2)	35 (26.9)	63 (48.5)	
Crude relative risk (95% CI)†					
Incident cancer	1.0	1.1 (0.8–1.5)	1.0 (0.7–1.4)	1.2 (0.9–1.6)	>0.2
P value	–	>0.2	>0.2	>0.2	
Incident CVD	1.0	3.7 (1.6–8.8)	5.1 (2.2–11.9)	9.2 (4.1–20.8)	<0.001
P value	–	0.003	0.001	0.001	
Adjusted relative risk (95% CI)‡					
Incident cancer	1.0	1.2 (0.8–1.6)	1.1 (0.7–1.5)	1.3 (0.9–1.9)	>0.2
P value	–	>0.2	>0.2	0.2	
Incident CVD	1.0	2.9 (1.2–7.1)	3.4 (1.4–8.2)	5.6 (2.3–13.2)	<0.001
P value	–	0.02	0.007	0.001	

* Case-patients and controls were matched for age and smoking status. CVD = cardiovascular disease.
† Adjusted for random assignment to vitamin E therapy and for random assignment to aspirin therapy.
‡ Adjusted for body mass index, hypertension, diabetes mellitus, hyperlipidemia, exercise, and parental history of coronary heart disease and for random assignment to vitamin E, aspirin, or both.

subsequently developed cardiovascular events had an increased baseline prevalence of hyperlipidemia, hypertension, diabetes, and obesity compared with controls who did not develop vascular events during follow-up.

Overall, median levels of CRP at baseline among women who subsequently developed cancer (2.6 mg/L [interquartile range, 1.1 to 5.9 mg/L]) were not significantly different from those of the control group (2.5 mg/L [interquartile range, 0.9 to 5.5 mg/L]) ($P > 0.2$). Furthermore, we observed no evidence of an association between baseline CRP level and the development of cancer in site-specific analyses evaluating carcinoma of the breast ($n = 223$), ovary or uterus ($n = 75$), colon ($n = 44$), lung ($n = 32$), hematopoietic system ($n = 31$), thyroid ($n = 14$), bladder ($n = 9$), brain ($n = 8$), or pancreas ($n = 8$); melanoma ($n = 31$); or other types of cancer ($n = 38$). In contrast, and consistent with previous work in this cohort for the end point of any vascular event (5), median CRP levels at baseline among women who subsequently developed cardiovascular disease (5.1 mg/L [interquartile range, 2.6 to 8.5 mg/L]) were significantly higher than those of the control group ($P < 0.001$).

Table 2 presents relative risks for developing either cancer or cardiovascular disease according to increasing quartiles of CRP levels obtained at study entry. As Table 2 shows, there was little evidence that baseline levels of CRP predicted incident cancer in either crude or adjusted analyses. We found similar results after additional correction for alcohol use and age at menarche (data not shown). In contrast, increasing quartiles of baseline CRP level were a strong marker of risk for incident cardiovascular disease in crude and adjusted analyses. For example, the adjusted relative risks from the lowest to the highest quartiles of baseline CRP levels were 1.0, 2.9, 3.4, and 5.6, respectively (*P* for trend < 0.001).

DISCUSSION

In this prospective study of apparently healthy middle-aged and older women, baseline plasma CRP concentrations were not significantly related to the incidence of future cancer but were a strong independent predictor of future myocardial infarction, stroke, and cardiovascular death.

We believe these data have importance for general medical practice for several reasons. First, our data corroborate the findings in several previous reports (2–6) that baseline levels of CRP predict future vascular events among apparently healthy men and women (2–6) and that CRP level adds to the predictive value of total and high-density lipoprotein cholesterol levels (5, 11). As a result of these earlier findings, outpatient screening for CRP has recently become available. However, if CRP is clinically nonspecific, as two recent studies evaluating all-cause mortality suggest (7, 8), then screening for this inflammatory marker might have reduced diagnostic utility. Thus, our finding that CRP appears to be specific for incident vascular disease but not for incident cancer has substantial clinical importance and suggests that data linking CRP level to overall death rates may have been due to the large contribution that vascular disorders make to all-cause mortality, particularly in the western world.

Second, the relative risks for future myocardial infarction or stroke observed among women in the top versus bottom quartile of baseline CRP in this analysis are somewhat greater than those previously reported from this cohort for the end point of any vascular event—an end point that included not only myocardial infarction, stroke, and cardiovascular disease mortality, but also coronary revascularization (5). Thus, these data also suggest that CRP level may be a stronger marker for events involving atherosclerotic plaque rupture and acute thrombosis than for events primarily involving progression of lesional stenosis. These epidemiologic data are thus consistent with the hypothesis that inflammation is an important determinant of plaque vulnerability (12).

Finally, we believe that our observation that CRP levels do not strongly predict future cancers is itself of pathophysiologic interest; this is of particular interest because levels of CRP and other inflammatory biomarkers are known to increase after development of certain malignancies (13, 14). As such, our data also suggest that the systemic inflammatory component of cancer previously reported in cross-sectional studies may be a late development in the genesis of that disease but is not likely to prove useful in determining risk among healthy persons.

Several limitations of our study deserve attention. Plasma CRP levels increase acutely in a wide variety of pathologic conditions, including febrile illness, various inflammatory states, and trauma (15). In our study, however, baseline levels of CRP were well below the standard thresholds associated with these acute-phase effects. Furthermore, participants in our study were free of known vascular disease, cancer, and other major inflammatory disorders at the time of study enrollment and blood collection. Thus, we believe that the presence of any of these conditions on an acute basis probably does not explain our observations. On the other hand, smoking, obesity, and older age are all positively associated with CRP levels (4). Nonetheless, in our study the relationships between baseline CRP levels and subsequent vascular risk were independent of these potential confounding factors. Although our decision to match case-patients and controls on smoking status limits our ability to evaluate the contribution of this variable to overall risk, it does not reduce the internal validity of these data with regard to CRP levels.

In conclusion, in this prospective, nested, case–control study of apparently healthy women, plasma CRP levels were not associated with incident cancer. In contrast, the relative risk for future cardiovascular events increased significantly with each increasing quartile of baseline CRP level.

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Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep, and endanger our survival; but should the kidneys fail in their task neither bone, muscle, gland nor brain could carry on.

Homer W. Smith
From Fish to Philosopher
Boston: Little, Brown; 1959

Submitted by:
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Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.–*The Editor*

Acquired Aplastic Anemia

Neal S. Young, MD

In aplastic anemia, hematopoiesis fails: Blood cell counts are extremely low, and the bone marrow appears empty. The pathophysiology of aplastic anemia is now believed to be immune-mediated, with active destruction of blood-forming cells by lymphocytes. The aberrant immune response may be triggered by environmental exposures, such as to chemicals and drugs or viral infections and, perhaps, endogenous antigens generated by genetically altered bone marrow cells. In patients with post-hepatitis aplastic anemia, antibodies to the known hepatitis viruses are absent; the unknown infectious agent may be more common in developing countries, where aplastic anemia occurs more frequently than it does in the West.

The syndrome paroxysmal nocturnal hemoglobinuria (PNH) is intimately related to aplastic anemia because many patients with bone marrow failure have an increased population of abnormal cells. In PNH, an entire class of proteins is not displayed on the cell surface because of an acquired X-chromosome gene mutation. The PNH cells may have a selective advantage in resisting immune attack. In contrast, the disease myelodysplasia can be confused with aplasia and can also evolve from aplastic anemia. The occurrence of cytogenetic abnormalities in patients years after presentation implies that genomic instability is a feature of this immune-mediated disease.

Aplastic anemia can be effectively treated by stem-cell transplantation or immunosuppressive therapy. Transplantation is curative but is best used for younger patients who have histocompatible sibling donors. Antithymocyte globulin and cyclosporine restore hematopoiesis in approximately two thirds of patients. However, recovery of blood cell count is often incomplete, recurrent pancytopenia requires retreatment, and some patients develop late complications (especially myelodysplasia).

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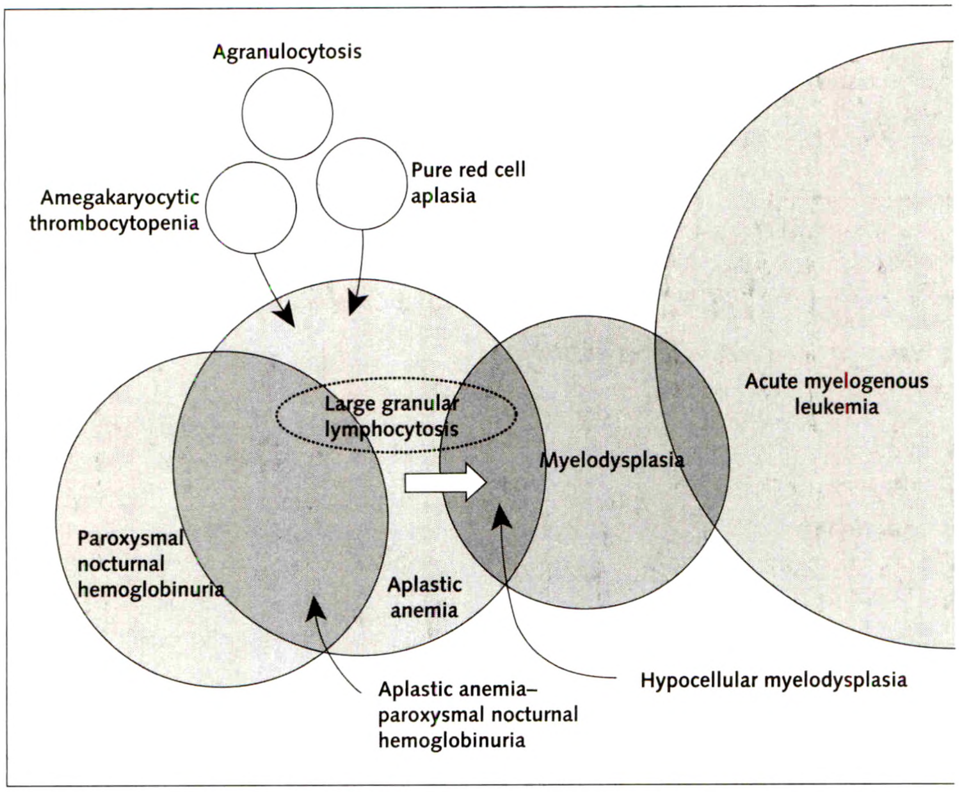
Aplastic anemia's long history, from its early description by Ehrlich (1) at the end of the 19th century, and the simplicity of its pathology, an empty bone marrow, have made it the paradigm of hematopoietic failure syndromes. Aplastic anemia is now increasingly recognized as being closely related to other hematologic diseases (**Figure** 1). Erythrocytes, granulocytes, and platelets, which are normally produced in the bone marrow, decrease to dangerously low levels. Blood cell counts determine presentation and prognosis. Anemia leads to fatigue, dyspnea, and cardiac symptoms; thrombocytopenia to bruising and mucosal bleeding; and neutropenia to sharply increased susceptibility to infection. When patients are treated with transfusions and antibiotics alone, survival rates are poor and related to the severity of the pancytopenia, as defined by the presence of two of three criteria: a neutrophil count less than 0.5×10^9 cells/L, a platelet count less than 20×10^9 cells/L, and a reticulocyte count less than 1%. When the neutrophil count is less than 0.2×10^9 cells/L, the disease is characterized as very severe. In the early 20th century, patients often died quickly of heart failure, profuse hemorrhage, or overwhelming infection. In the modern era of erythrocyte and platelet transfusions, the most common causes of death are recurrent bacterial sepsis or fungal invasion of critical organs secondary to refractory granulocytopenia.

Historically, aplastic anemia has been strongly associated with exposure to chemicals and drugs in the environment, giving the disease a social impact disproportionate to its incidence (2). The recognition of bone marrow failure in workers exposed to benzene led to heroic industrial hygiene crusades by Alice Hamilton and Harrison Martland in the United States in the 1920s and 1930s. In the late 1940s and early 1950s, an epidemic of aplastic anemia appeared to follow the introduction of chloramphenicol, and the disease has been linked to many classes of pharmaceuticals widely used in medical practice (**Table**). Because aplastic anemia has become such a feared disorder as a result of its association with common drug use, even a few cases can have a profound effect on new drug development by the pharmaceutical industry. Also, this believed association with numerous, diverse possible causes, from chemicals and drugs to hepatitis, infectious mononucleosis, pregnancy, and collagen vascular processes (for example, eosinophilic fasciitis), has led to the belief that there also are numerous and different mechanisms of disease.

However, we now have a plausible, unified model of the pathophysiology of aplastic anemia, drawn from both compelling clinical observations of therapeutic efficacy and systematic laboratory experimentation. The early, successful use of bone marrow transplantation to cure aplastic anemia implicated a stem-cell deficiency.

Figure 1. **Venn diagram showing possible relationships among bone marrow failure syndromes.**


Agranulocytosis
Amegakaryocytic thrombocytopenia
Pure red cell aplasia
Large granular lymphocytosis
Acute myelogenous leukemia
Myelodysplasia
Paroxysmal nocturnal hemoglobinuria
Aplastic anemia
Aplastic anemia–paroxysmal nocturnal hemoglobinuria
Hypocellular myelodysplasia

These syndromes include clonal diseases (paroxysmal nocturnal hemoglobinuria, myelodysplasia, and large granular lymphocytosis); and single hematopoietic lineage deficiency diseases (agranuloyctosis, pure red-cell aplasia, and amegakaryocytic thrombocytopenia); note especially the areas of overlap between aplastic anemia and paroxysmal nocturnal hemoglobinuria and myelodysplasia.

Later, responses to immunosuppressive therapies pointed to an immune mechanism of hematopoietic failure. As aplastic anemia is progressively demystified, questions of some biological interest emerge. These are relevant to bone marrow failure as well as to our conceptions of autoimmune diseases of other organ systems and to the relationship of immune mechanisms to malignant transformation.

IMMUNE PATHOPHYSIOLOGY OF APLASTIC ANEMIA

Most cases of acquired aplastic anemia can be pathophysiologically characterized as T-cell–mediated, organ-specific destruction of bone marrow hematopoietic cells (4). In an individual patient, the aberrant immune response can sometimes be linked to a viral infection or to drug or chemical exposure (**Figure 2**). There is much less evidence for other mechanisms, such as direct toxicity for stem cells or a deficiency of stromal-cell or hematopoietic growth factor function. Furthermore, the variability in clinical course and response to treatment can be explained by the quantitative degree of stem-cell destruction and qualitative variations in immune response.

Hematopoietic Failure

That failure of blood cell production was responsible for the empty bone marrow was a prescient conclusion of the earliest observers of the "yellow fat" of the bony spaces and the absence of the morphologically diverse precursors of mature blood elements—still so striking on examination of bone marrow aspirate smears or core biopsy specimens (5). Magnetic resonance imaging of the vertebrae shows uniform replacement of marrow with fat. Immature hematopoietic cells can also be quantitated by fluorescent-activated flow cytometry, which can detect the CD34 cell antigen, an adhesion protein present on less than 1% of normal bone marrow. CD34 cells are almost absent in

Table. **Drugs Associated with Aplastic Anemia in the International Aplastic Anemia Agranulocytosis Study***

Drug	Stratified Risk Estimate (95% CI)	Multivariate Relative Risk Estimate (95% CI)
	%	
Nonsteroidal analgesics		
Butazones	3.7 (1.9–7.2)	5.1 (2.1–12)
Indomethacin	7.1 (3.4–15)	8.2 (3.3–20)
Piroxicam	9.8 (3.3–29)	7.4 (2.1–26)
Diclofenac	4.6 (2.0–11)	4.2 (1.6–11)
Antibiotics		
Sulfonamides†	2.8 (1.1–7.3)	2.2 (0.6–7.4)
Antithyroid drugs	16 (4.8–54)	11 (2.0–56)
Cardiovascular drugs		
Furosemide	3.3 (1.6–7.0)	3.1 (1.2–8.0)
Psychotropic drugs		
Phenothiazines	3.0 (1.1–8.2)	1.6 (0.4–7.4)
Corticosteroids	5.0 (2.8–8.9)	3.5 (1.6–7.7)
Penicillamine	∞	
Allopurinol	7.3 (3.0–17)	5.9 (1.8–19)
Gold‡	29 (9.7–89)	–

* Relative risk quantitates the relative increase in the incidence of aplastic anemia in users of specific drugs compared with nonusers. The absolute risk, however, for developing aplastic anemia as a result of drug use is very small. Aplastic anemia is rare and is a very infrequent complication of drug use relative to the large number of people using drugs. Adapted with permission from Kaufman et al. (3).

† Does not include trimethoprim–sulfonamide combination.

‡ No multivariate relative risk estimate because of insufficient number of exposed patients and controls.

aplastic anemia. Progenitor cells capable of forming erythroid, myeloid, and megakaryocytic colonies in tissue culture are greatly reduced, and assays of very primitive, quiescent, hematopoietic cells that are closely related if not identical to stem cells show a similar consistent and severe deficit. By extrapolation from such functional studies of aplastic bone marrow, it is likely that patients present with pancytopenia when stem-cell and progenitor-cell populations have decreased to approximately 1% or less of normal. Such a profound deficiency has important qualitative consequences, as reflected in the shortened telomere length of granulocytes of patients with aplastic anemia (6).

Immune Destruction

The efficiency of immune system destruction of blood-forming cells is obvious in "runt disease" in animals and in transfusion-associated graft-versus-host disease (GVHD) in humans (7). In these syndromes, small numbers of alloreactive T cells produce fatal aplastic anemia, and in the mouse model, we know that stem-cell destruction is rapid and almost complete. Much laboratory data support the hypothesis that, in most patients with acquired aplastic anemia, lymphocytes are responsible for the destruction of the hematopoietic cell compartment (4).

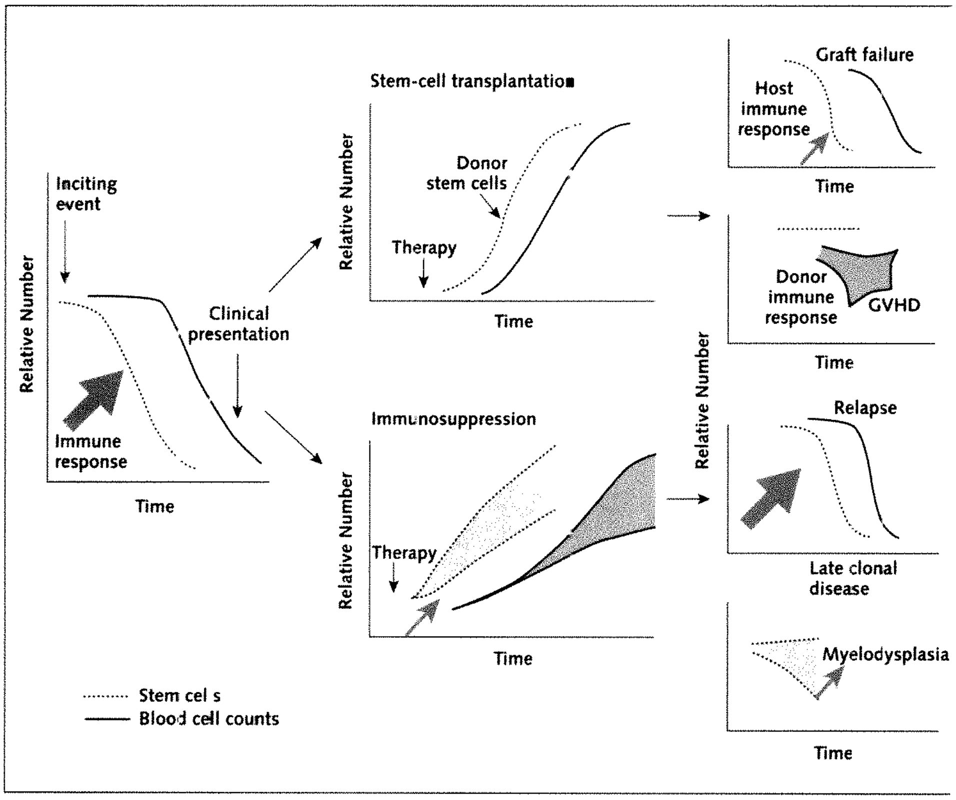
Early experiments showed that the patients' lymphocytes suppressed hematopoiesis. These cells produced a soluble, inhibitory factor that was eventually identified as interferon-γ. Activation of a TH1-type T-cell response has been inferred from immunophenotypic characterization of T cells and excessive production of interferon, tumor necrosis factor, and interleukin-2. Detection of intracellular interferon-γ in patient samples by flow cytometry may correlate with responsiveness to immunosuppressive therapy and may predict relapse (8). Altered immunity results in destruction, specifically Fas-mediated CD34 cell death, and in activation of intracellular pathways leading to cell-cycle arrest. Immunity is local and has been modeled in tissue culture when low concentrations of interferon-γ are secreted into the marrow microenvironment. In an animal model, bone marrow failure after injection of alloreactive lymphocytes can be prevented by treatment with a monoclonal antibody to interferon-γ (9).

The nature of the antigen or antigens driving the pathologic immune response is unknown. At the molecular level, lymphocytes in aplastic anemia show similarity to T cells in multiple sclerosis, diabetes, and other related illnesses. Characterization of the T-cell–receptor β chain of activated lymphocytes shows that the immune response is oligoclonal, with a relatively limited number of active clones infiltrating the marrow. Some immune responses may be public, that is, shared among patients with the same histocompatability background (10). Immortalized T-cell clones in the laboratory should allow the definition of antigenic peptides, and knowledge of the antigen-binding sequence of the involved T-cell–receptor β chain could provide a molecular method to distinguish patient subgroups and to assess the effectiveness of immunosuppressive therapies.

THE DIFFICULT DIFFERENTIAL DIAGNOSIS OF BONE MARROW FAILURE

The presence of fatty bone marrow on biopsy indicates aplasia; however, marrow hypocellularity can occur in other hematologic diseases. New diagnostic tests have profoundly affected the differential diagnosis and our understanding of bone marrow failure (**Figure** 1). The distinction between

Figure 2. **Pathophysiology and treatment of aplastic anemia.**



The left panel illustrates induction of disease by an inciting event (for example, viral infection or chemical exposure) followed by an aberrant immune response that leads to destruction of hematopoietic stem cells and progenitor cells. When destruction is sufficiently advanced, pancytopenia and clinical disease result. Hematopoietic stem-cell transplantation both replaces the missing hematopoietic cells and is potently immunosuppressive. Immunosuppression reduces or eliminates the aberrant immune process. Late complications of transplantation include graft failure or relapse (presumably caused by resurgent autoimmune attack) and, more frequently, graft-versus-host disease (*GVHD*) and infection. Immunosuppressive therapies based on antithymocyte globulin can often partially or fully improve blood cell counts and stem-cell recovery, but patients are susceptible to recurrence of pancytopenia or the development of other hematologic diseases (such as myelodysplasia).

acquired and constitutional forms of aplastic anemia has been sharpened by specific assays for the chromosomal susceptibility to certain chemical cross-linking agents that characterizes Fanconi anemia. Although it usually presents in childhood, Fanconi anemia can be diagnosed well into adulthood, even in the absence of skeletal and urogenital anomalies (11). Other constitutional syndromes must be inferred from a suspicious pedigree or typical physical stigmata (the abnormal nails of dyskeratosis congenita or the neurologic signs of the ataxia–pancytopenia syndrome). As with Fanconi anemia, genetic testing should ultimately be possible for these diseases.

Hypocellular Myelodysplasia

Cytogenetic testing of marrow cells is routine, but the interpretation of results can be controversial. Chromosomes are normal in typical aplastic anemia, but aneuploidy or structural abnormalities are relatively common in the myelodysplastic syndromes. When the marrow is normal or hypercellular and hematopoietic cells are obviously dysmorphic, myelodysplasia is easily distinguished from aplastic anemia. However, in perhaps 20% of cases, marrow samples are hypocellular; furthermore, morphologic changes may be subtle or unconvincing, and chromosome testing may have normal results or be unsuccessful because of low numbers of cells (12). The differential diagnosis is further confused by the evolution of treated aplastic anemia to myelodysplasia (see following discussion) and the responsiveness of patients with some forms of myelodysplasia (especially when bone marrow failure rather than preleukemia is the dominant clinical feature) to the same types of immunosuppressive therapy that are effective for aplastic anemia (13). Experts may disagree on the correct diagnosis when trying to distinguish aplastic anemia from myelodysplasia in an individual patient, and there is no consensus at present as to whether certain chromosomal abnormalities, such as trisomy 8, exclude the diagnosis of immune-mediated bone marrow failure.

Large granular lymphocytic leukemia can also be a concurrent diagnosis in empty or dysplastic bone marrow. Large granular lymphocytes can be recognized by their distinctive phenotype on microscopic examination of the blood; their distinctive pattern of staining on flow cytometry; and their very specific patterns of T-cell receptor rearrangement, which is evidence of monoclonal expansion of a population of antigen-driven T cells.

Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria

A very strong clinical relationship exists between aplastic anemia and paroxysmal nocturnal hemoglobinuria (PNH). In PNH, an abnormal hematopoietic stem cell gives rise to an expanded population of mature red blood cells, granulocytes, and platelets, all of which lack an entire class of distinctive cell-surface proteins. These proteins attach to the cell not through the usual transmembrane hydrophobic domain but by a glycolipid moiety that is covalently bound to the protein after it is synthesized. The genetic basis of PNH is an acquired mutation in *PIG-A*, an X-chromosome gene that aborts synthesis of the glycosylphosphatidylinositol (GPI) anchor structure. Deficiency of the GPI-anchored protein CD59 explains intravascular hemolysis in PNH, which results from the inability of erythrocytes to inactivate the surface complement. Absence of GPI-anchored proteins is easily detected by flow cytometric methods applied to both erythrocytes and leukocytes; the Ham and sucrose tests are now obsolete.

It has long been known that some patients with PNH will develop bone marrow failure and, conversely, that PNH may be observed as a "late clonal event" years after the diagnosis of aplastic anemia (see following discussion). However, flow cytometry has revealed that a large proportion of patients with bone marrow failure have expansion of a hematopoietic PNH clone at clinical presentation. In my group's most recent analysis, PNH cells were identified in 42% of patients with aplastic anemia (and 23% of those with myelodysplasia) early in the disease process and before any treatment (14). Indeed, PNH is only occasionally a late occurrence in aplastic anemia. Conversely, even patients with predominantly hemolytic PNH have evidence of hematopoietic insufficiency in progenitor cell assays. Given this striking degree of clinical and functional overlap, it hardly seems accurate to continue to describe PNH as only an association with aplastic anemia.

What accounts for the expansion of the progeny of a genetically altered stem-cell population in an immune-mediated disease? The results of "knock-out" of the homologous *pig-a* gene in the mouse, as well as the finding of tiny PNH clones in many normal persons, indicate that the somatic mutation is required but not sufficient to explain clonal expansion. That clonal expansion may be linked to the immune pathophysiology is implied by the strong association of HLA-DR2 with PNH and by the presence of a PNH clone as a positive predictive factor for responsiveness to immunosuppressive therapy (15). However, the exact relationship is unclear. One attractive explanation is resistance of the PNH clone to immune attack, which would produce a selective advantage for these cells. This hypothesis is supported by the finding that in a patient with PNH, the PNH cells appear to be capable of normal growth, but the normal bone marrow cells are at a proliferative disadvantage and appear to be dying as a result of Fas-mediated apoptosis (16, 17). A second possibility is that the GPI-anchored proteins play an antigenic role in the initiation and maintenance of the immune attack on hematopoietic cells (18). An individual protein may be a common culprit, but GPI-anchored proteins may be more globally immunogenic, perhaps resulting from altered degradation of proteins that are retained in the cytoplasm in *PIG-A*–deficient cells rather than being displayed on the cell surface as in normal cells, with presentation of their peptides in a class I rather than class II histocompatability antigen context.

AN INFECTIOUS CAUSE FOR APLASTIC ANEMIA?

Mainly on the basis of epidemiologic data, diseases such as multiple sclerosis and type 1 diabetes mellitus have been suspected of having infectious triggers. Animal models and in vitro data support various mechanisms that might lead to a breakdown in tolerance for normal tissues after infection, including molecular mimicry, antigenic spread, and danger signals elicited by a microbe. For immune-mediated bone marrow failure, one clinical syndrome strongly suggests an inciting infectious cause. Post-hepatitis aplastic anemia typically occurs in young, previously healthy males who have self-limited but severe liver inflammation with very high serum aminotransferase and bilirubin levels; profound pancytopenia follows several weeks later (19). The blood cell count depression is so severe and sustained that post-hepatitis aplastic anemia has been considered an absolute indication for early stem-cell transplantation; however, both the marrow and liver improve with immunosuppressive therapies as well.

The presumed infectious cause of aplastic anemia remains mysterious. Serologic testing consistently yields negative results for the known hepatitis viruses (A, B, and C) and for putative agents, such as hepatitis G and transfusion-transmitted viruses (20). Parvovirus B19 has been implicated in a few cases. This virus directly affects blood cell production but almost always only as a result of highly specific infection of erythroid progenitor cells (21). B19 parvovirus can also occasionally produce mild hepatitis, but its role in more fulminant hepatitis remains uncertain (22).

Seronegative fulminant hepatitis is the most common cause of liver failure in children, and, remarkably, more than one third of patients undergoing transplantation for this form of liver failure develop peri-transplantation aplastic anemia or marrow depression (23). Acute seronegative hepatitis also is often associated with serologic evidence of immune activation, particularly autoantibodies (24). Acute seronegative hepatitis is infrequent in the United States but is more common in liver clinics in developing countries; this is consistent with a presumed enteric mode of transmission. In Hanoi, for example, acute seronegative hepatitis accounted for about 20% of cases (25) compared with less than 3% in the United States (26). This geographic variation parallels rates of aplastic anemia. Large prospective studies established an annual incidence of 2 new cases per 1 million population in Europe and Israel. In Asia, recent similarly conducted studies in Thailand (27) and China (28) have determined the incidence to be about three times that in the West.

CHOOSING TREATMENTS

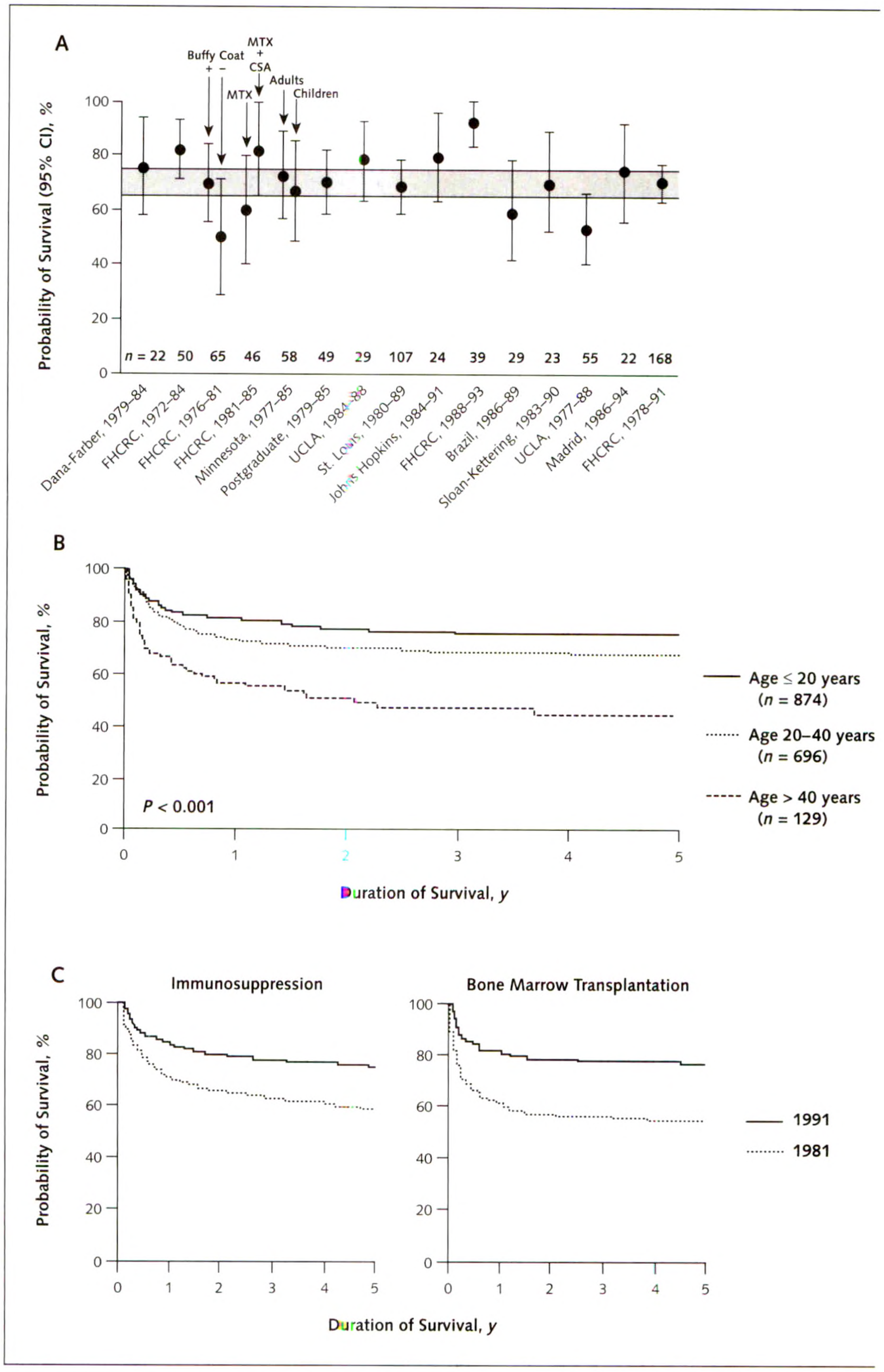
The underlying pathology of acquired aplastic anemia has been addressed by replacing the marrow through stem-cell transplantation or by quelling lymphocyte attack through immunosuppressive therapies (**Figure** 2). These approaches differ markedly in applicability, short- and long-term risks (29, 30), and the completeness and durability of hematologic recovery.

Hematopoietic Stem-Cell Transplantation

Bone marrow and, more recently, peripheral blood stem-cell transplantation from a histocompatible sibling usually cure the underlying bone marrow failure (**Figure** 3). Survival rates have been reported to be as high as 90% from a single, experienced institution (33) and at 75% to 80% for registry data, which reflect more general experiences (34). Mortality rates for the first 100 days after transplantation have decreased, probably as a result of less graft rejection and better control of infections. Graft-versus-host disease, the frequency and severity of which correlate with patient age, continues to limit the success of transplantation. In most analyses, adults have lower survival rates compared with children. In one large study, 41% of 212 patients surviving for more than 2 years after transplantation had developed chronic GVHD, and the mortality rate was three times higher than the rate for patients without this complication (34); GVHD contributed to earlier deaths as well.

Allogeneic transplantation is available to only a minority of patients because about 70% will lack a suitably matched sibling donor. Many more donors are available outside the family and can now be located through large registries in the United States and Europe. Relatively good results have been achieved at Children's Hospital in Milwaukee, Wisconsin, where treatment consists of T-cell depletion of the graft combined with cytosine arabinoside, cyclophosphamide, and total-body irradiation. Survival at a median follow-up of about 3 years in 28 children was 54%, despite the heavy transfusion burden and previous treatment; GVHD occurred infrequently (35, 36). Results elsewhere have been more disappointing, especially in adults, as a result of high rates of graft rejection, GVHD, and infection caused by delayed immune system reconstitution. In general, survival has been about half that observed with standard transplants: 29% (37) to 37% (38). Older patients poorly tolerate the rigorous conditioning regimens required for engraftment. Even in children, these regimens are likely to exact a delayed toll of late malignant disease. In aplas-

Figure 3. **Results of treatment in patients with acquired aplastic anemia.**



A. Allogeneic bone marrow transplantation. Data are presented from individual hospital series in peer-reviewed publications from 1991 to 1997. The shaded area represents the 5-year probability of survival (with the same confidence intervals) of patients reported to the International Bone Marrow Transplant Registry (IBMTR) during this period. Adapted with permission from Horowitz (31); original source provides detailed information on each series. B. The continuing influence of age on survival, as reflected in IBMTR data. Adapted with permission from Horowitz (31). C. Comparative probability of survival after immunosuppression and bone marrow transplantation. The data are for patients reported to the Working Party on Severe Aplastic Anemia of The European Group for Blood and Marrow Transplantation in the 1980s and 1990s. Adapted with permission from Bacigalupo et al. (32); CSA = cyclosporine; FHCRC = Fred Hutchinson Cancer Research Center; MTX = methotrexate; UCLA = University of California, Los Angeles.

tic anemia, malignant tumors occur at a higher-than-expected rate in patients undergoing standard conditioning (39, 40); intensive chemotherapy and radiation therapy used in unrelated-donor regimens may increase this risk (41).

Immunosuppression

Immunosuppression is used in patients who are not candidates for stem-cell transplantation because of older age or lack of a donor. Both horse and rabbit antithymocyte globulin (ATG) are licensed in the United States. Hematologic responses, which are usually equivalent to sufficiently improved blood cell counts, occur in 40% to 50% of patients treated with ATG; such patients no longer require transfusions and are not susceptible to infection (29, 42). The addition of cyclosporine to ATG has improved response and survival. In studies in Europe (43) and the United States (44), response rates have been 70% to 80%, and the 5-year survival rate in the responding patients has been 80% to 90%. Combined treatment with cyclosporine and ATG versus ATG alone shows substantial benefit for children and patients with absolute neutropenia. As a single agent, cyclosporine is inferior to ATG (45).

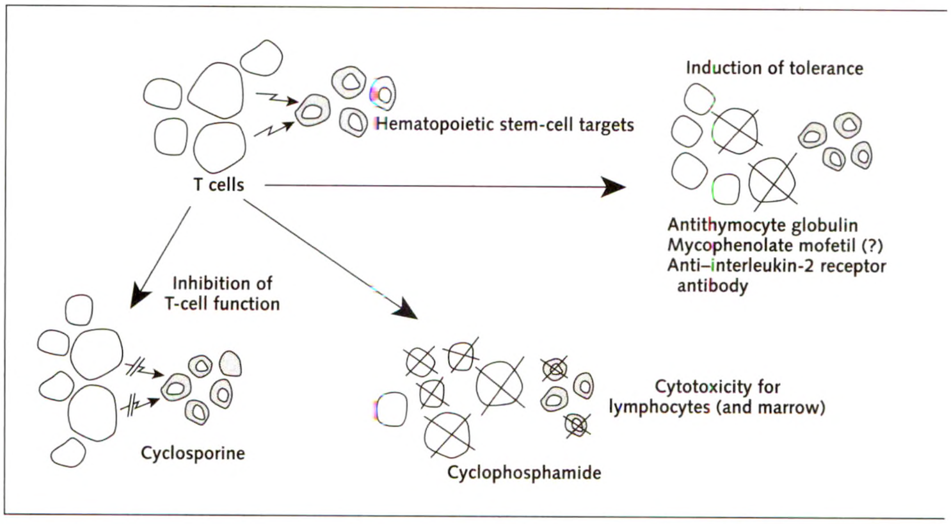
Many patients with aplastic anemia are not adequately treated with a single course of ATG followed by several months of cyclosporine. Relapse is not infrequent. Blood cell counts may decrease when cyclosporine is discontinued but then increase when the agent is reinstituted. In some patients, maintaining blood cell counts may depend on continued administration of low-dose cyclosporine. Frank recurrence of pancytopenia prompts a second course of ATG. However, long-term prognosis does not appear to be affected by relapse. Patients who respond to immunosuppression often continue to have blood cell counts that, while adequate for full activities, remain below normal. Incomplete responses, frequent relapses, and cyclosporine dependence are most likely evidence of chronic immune system effects on a hematologically compensated bone marrow. An additional problem is the development of late clonal diseases (see following discussion).

The effectiveness of immunosuppressive therapy in aplastic anemia was first observed when ATG was used in the conditioning regimen before transplantation: Some patients who rejected the graft recovered their own marrow function. The same effect was seen with cyclophosphamide. Small numbers of patients at Johns Hopkins University, Baltimore, Maryland, were treated with high-dose cyclophosphamide without stem-cell rescue during intervals in the 1980s, when ATG was temporarily not available; results were promising (46). Outcomes of the same treatment in 19 patients have recently been published (47). The hematologic response rate was similar to that seen with ATG combined with cyclosporine; more important, neither relapse nor evolution to PNH or myelodysplasia was observed. However, a randomized trial conducted at the National Institutes of Health (NIH) that compared ATG with cyclophosphamide (both study groups included cyclosporine) was terminated prematurely because of excessive toxicity, severe fungal infections, and deaths in the group that received cyclophosphamide (48). Cyclophosphamide is a much more aggressive immunosuppressive treatment than ATG. Absolute neutropenia can persist for many weeks, necessitating prolonged courses of antibiotics and even granulocyte transfusions. Thus, extremely severe disease, with its poorer immediate prognosis, may be iatrogenically induced. It is disappointing that some patients in the NIH study who received high-dose cyclophosphamide have relapsed or developed cytogenetic abnormalities and that PNH clones were unaltered by treatment (49).

One new strategy is based on inducing immunologic tolerance (**Figure 4**). Antithymocyte globulin reduces lymphocyte counts, but transiently and modestly compared with the effect of cytotoxic chemotherapy. Part of the beneficial activity may be the induction of tolerance, perhaps by specific deletion of activated lymphocytes. Indeed, the concurrent use of cyclosporine, which blocks T-cell activation, may blunt the efficacy of ATG (50, 51). In our new protocol, we delay the introduction of cyclosporine and add a novel immunosuppressive drug, mycophenolate mofetil. This drug, by inhibiting inosine monophosphate, is cytotoxic for cycling T cells. Activated lymphocytes should be subject to elimination by their characteristic cell-surface antigens (recognized by ATG) and their mitotic activity.

Other mild but more specific forms of immunosuppression might also be effective. For example, ATG contains antibody specificities for the interleukin-2 receptor, which is present on activated lymphocytes. My colleagues and I are testing a commercially available monoclonal anti-

Figure 4. **Immunosuppressive therapies.**


Induction of tolerance
Hematopoietic stem-cell targets
T cells
Antithymocyte globulin
Mycophenolate mofetil (?)
Anti–interleukin-2 receptor antibody
Inhibition of T-cell function
Cytotoxicity for lymphocytes (and marrow)
Cyclosporine
Cyclophosphamide

Activated T cells, shown as enlarged, attack and destroy hematopoietic stem-cell targets. Some drugs inhibit lymphocyte function. Others are broadly lymphocytotoxic. Laboratory and animal data show that agents relatively selective for activated lymphocytes can induce tolerance by eliminating functionally active T-cell clones. Antithymocyte globulin, cyclosporine, and cyclophosphamide have been used to treat aplastic anemia, alone and in combination.

body to this receptor in patients with moderate aplastic anemia. Monoclonal antibodies, recombinant soluble cytokine receptors, and new immunosuppressive drugs (for example, rapamycin) deserve examination in immune-mediated bone marrow failure syndromes.

Refractory Pancytopenia

One quarter to one third of patients do not respond to ATG and cyclosporine. In addition, in my most recent analysis of 122 patients receiving this protocol, both survival and evolution to late clonal diseases in patients who responded were inversely correlated with the degree of improvement in blood cell counts at 3 months (52). At present, no clear guidelines are available for the treatment of refractory or poorly responsive aplastic anemia. Multiple courses of immunosuppression are commonly administered at European centers. In a recent study from Italy, most patients who received rabbit ATG after unsuccessful treatment with horse ATG became transfusion independent (53). These results suggest that primary treatment failure should not necessarily be interpreted as indicating a nonimmune mechanism of disease. Nevertheless, in some patients, the marrow may be too severely damaged to allow recovery. Because of the poor long-term outlook, patients in whom immunosuppression fails should consider unrelated stem-cell transplantation.

There is little justification for either a therapeutic trial of corticosteroids as primary treatment or for their long-term use to prevent bleeding. Patients with aplastic anemia seem to be particularly susceptible to one of the severe complications associated with corticosteroid use—aseptic necrosis (54). Hematopoietic growth factors are not appropriate as first-line treatment for severe aplastic anemia. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor can increase granulocyte counts in aplastic anemia, but this effect is almost always transient and rarely occurs in patients with profound neutropenia (55). In addition, G-CSF does not improve the response or survival rates in patients receiving standard immunosuppressive therapy (56). However, growth factors can occasionally be useful in refractory aplastic anemia. Clinically meaningful improvement in blood cell counts occasionally has been seen after prolonged administration of G-CSF, erythropoietin, and stem-cell factor, usually in some combination (57–59).

A few patients have a choice of allogeneic transplantation or immunosuppressive therapy. For patients who are "biologically" assigned to transplantation because they have an appropriately matched sibling, morbidity and mortality rates have been compared with those of patients receiving immunosuppression (although this is an imperfect surrogate for a true randomized, controlled trial because medical and socioeconomic factors may preclude a specific treatment). Analyses of large databases have not shown major general differences in outcomes between the two therapeutic approaches (**Figure 3C**) (32). Nevertheless, transplantation is preferable for certain defined subgroups: most children and patients with very severe neutropenia. Patients in whom immunosuppressive therapy fails have later undergone successful transplantation from matched siblings or from unrelated donors.

EVOLUTION OF APLASTIC ANEMIA TO OTHER HEMATOLOGIC DISEASES AND LATE CLONAL EVENTS

As patient survival has improved, so too has the opportunity to observe the long-term course of bone marrow failure. Evolution of aplastic anemia to another hematologic disease has been reported in a substantial minority of patients undergoing immunosuppressive therapy. In a large European series of more than 200 patients, the actuarial risk for developing myelodysplasia and leukemia at 7 years was 15% (60). In a series of more than 100 patients closely followed at the NIH Clinical Center, my colleagues and I found the actuarial risk for late clonal events among responders at 6 to 10 years after treatment to be 19%. It should be noted that immunosuppression by itself is not the cause of late clonal events; similar clinical progression has been seen in patients treated with androgens (61).

Appearance of a dysmorphic, cellular marrow on an aspirate smear with or without new chromosomal abnormalities leads to the diagnosis of myelodysplasia. The original diagnosis of aplastic anemia may be questioned when such an abnormal bone marrow is observed within weeks or a few months after presentation or treatment. In addition, aplastic anemia and myelodysplasia may share the same immune pathophysiology for the development of pancytopenia. Young patients with some forms of myelodysplastic syndromes, especially those with hypocellular marrow and normal cytogenetic findings, respond well to ATG or cyclosporine (62). As in aplastic anemia, laboratory data can show lymphocyte activation and excessive production of lymphokines, with resulting increased apoptosis of hematopoietic cells (13).

The significance of specific cytogenetic findings in aplastic anemia varies. Some chromosomal abnormalities may be only transient. Patients with trisomy 8 are often dependent on a long-term course of cyclosporine to maintain normal blood cell counts. Their prognosis is relatively good. Monosomy 7, in contrast, is almost always a harbinger of refractory pancytopenia and carries a high likelihood of leukemic transformation.

Chromosomal abnormalities can develop years after blood cell counts have improved with immunosuppressive therapy, even though results of intervening multiple cytogenetic studies were normal. This pattern suggests genomic instability. A relationship between chronic inflammation and malignancy has been a subject of speculation and study for many decades. Analogous clinical relationships exist between chronic hepatitis and hepatocellular carcinoma, ulcerative colitis and colon cancer, and chronic GVHD and various malignant tumors. In aplastic anemia, abnormal clones may be selected for expansion under conditions of hematopoietic stress (for example, sustained high hematopoietic growth-factor concentrations). Alternatively, a chronic inflammatory environment may itself be mutagenic as a result of increased concentrations of reactive oxygen species or cell damage short of complete apoptosis.

ACQUIRED APLASTIC ANEMIA AS A HEMATOLOGIC DISEASE AND AS AN IMMUNE-MEDIATED SYNDROME

In the 20th century, our understanding of the origin of aplastic anemia and the definitive and supportive treatment of patients improved enormously. Unfortunately, stem-cell destruction may be very advanced by the time the patient presents with pancytopenia. Restoration of hematopoiesis by stem-cell transplantation or suppression of the pathologic immune response to allow the patient's own marrow to recover are both effective. Improvements in methods for monitoring hematopoiesis and immune system activity and especially in the use of immunomodulatory drugs should be of clinical benefit. Major research questions remain concerning the nature of inciting antigens and the determinant of the aberrant immune response, as well as the fundamental pathophysiologic relationships among aplasia, dysplasia, and PNH.

Acquired aplastic anemia is usually immune mediated. It shares clinical and epidemiologic features and pathophysiologic mechanisms with other human autoimmune diseases in which restricted numbers of T-cell clones effect severe, tissue-specific destruction. Autoimmune diseases occur in young persons, often with only a modest familial disposition, if any. Geographic variation may be observed, and precipitating events (for example, viral infection) have been suggested because of the peculiar epidemiologic features of autoimmune diseases. Studies in humans and animal models have suggested that limited numbers of antigens may drive this highly efficient and selective destructive process. The affected target cells have determined not only the clinical presentation but also the prognosis for recovery or irreparable loss of organ function and relapse. Historically, emphasis on end-organ damage has meant that different subspecialists have confronted each of these diseases. Improvement in our understanding and especially in our ability to measure the underlying immune pathophysiologic mechanisms—combined with the development of new immunosuppressive and immunomodulatory drugs—suggests that the common immunologic pathways of organ destruction can be addressed across subspecialty boundaries.

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Chambers

Last night John Comet received first warning,
Pain the flashing sign of tissue damage,
And called his doctor in the early morning.

"Each part," said my teacher once in college,
"Of the anatomy is a piece of your car.
Pain's the red oil light." Last spring I merely turned

My ankle and this auto-portrait only went so far.
Not so much like the Audi's blinking, I learned,
This warning was a scream, slip of the steak knife,

Wrench of the steering wheel, airplane's lurch,
Momentary reminder of this poised life.
But this story, you see, is my father's,

Wandering through empty rooms, looking for
The morning papers. This angina, he seemed to tell us,
Was no flapping fanbelt or fuel leak. At his heart's core

Was pressure and dis-ease, a push from this
Narrow airy beam into the realm of stones,
Clammy, close, then the fated shove.

And as for the language of this lesson,
We must insist on, not piston engines
Failing, but four tortured chambers echoing
In the hollowed, fabled resting place of love.

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EDITORIAL

Avoiding Nocturnal Hypoglycemia: Consideration of an Extra Injection at Bedtime

While sleeping, how do you replace insulin, a life-sustaining hormone with a narrow therapeutic range whose requirements change throughout the night? This challenge has faced patients with type 1 diabetes mellitus and their physicians since the first use of purified insulin for subcutaneous injection in 1922. The Diabetes Control and Complications Trial (1) demonstrated the magnitude of this challenge, showing that intensive insulin therapy not only delays microvascular complications but also increases the risk for hypoglycemia by roughly threefold, with more than half of the episodes occurring during sleep (2).

It has long been assumed that the risk for nocturnal hypoglycemia is lower when long-acting insulin is given at bedtime (split-dose regimen) rather than at the evening meal (mixed-dose regimen) (3). The risk is presumed lower with bedtime insulin because, in theory, when the long-acting insulin is given at dinnertime, it will peak earlier in the night, closer to the nadir of insulin needs (3). Thus, it is of interest that the Diabetes Control and Complications Trial found increased nocturnal hypoglycemia risk in its intensive treatment group, which was receiving a split-dose regimen, compared with the control group, which was receiving a mixed-dose regimen. The increased risk for nocturnal hypoglycemia in the intensive treatment group was naturally ascribed to the intensive glycemic goals rather than to the split-dose regimen of the intervention group; however, this conclusion lacked proof.

In this issue, Fanelli and colleagues (4) report on their study, which tested this assumption directly by comparing a split-dose regimen with a mixed-dose regimen; both groups had intensive glucose targets. This prospective, open-label study was small, following 22 adults with type 1 diabetes mellitus randomly assigned to the two 4-month crossover treatment groups. Blood glucose levels were measured daily before each injection and at bedtime and every other night at 3:00 a.m. The investigators found more than a 60% decline ($P = 0.002$) in the frequency of nocturnal hypoglycemia during split dosing compared with during mixed dosing.

A 60% reduction in the vexing entity of nocturnal hypoglycemia is welcome. At its frightening extreme, nocturnal hypoglycemia may precipitate an unexpected nighttime seizure or coma. However, even in its more common, asymptomatic form, which goes unnoticed, the consequences are not trivial and can include hypoglycemia unawareness (5) and worsening of daytime metabolic control (6, 7). Several of these issues were examined by Fanelli and colleagues (4), who observed improvements during the split-dose phase, as expected. Fasting blood glucose values and overall glycemic control improved during split-dose treatment. At the end of each treatment phase, the investigators assessed responses to insulin-induced hypoglycemia. The threshold and amplitude of autonomic responses were improved in the split-dose phase. This may translate to a degree of protection against severe hypoglycemia.

The authors conclude that "whenever possible, patients with type 1 diabetes should be given the split insulin regimen in the evening" (4). This statement is overly strong, especially considering the very limited sample studied. The study participants had a narrow age range (mean [±SD], 29 ± 3 years). Known risk factors for nocturnal hypoglycemia include a history of severe hypoglycemia, lower hemoglobin A_{1c} value, age younger than 5 years, and long duration of diabetes (8–10). Unfortunately, this study excluded patient groups at highest risk for hypoglycemia. Specifically, patients with a history of severe hypoglycemia were excluded, and patients outside of young adulthood were not included to any appreciable degree. These groups are most in need of evidence to clarify whether split dosing could reduce their high risk for nocturnal hypoglycemia.

A minor detractor of these data is that the study cohort was already receiving intensive, split-dose insulin regimens before the study. Thus, presumably, insulin doses were already optimized for glycemic control and avoidance of nocturnal hypoglycemia for split dosing. In contrast, the mixed-insulin doses had to be determined de novo during the study. To lessen this confounder, the authors studied only the last month of each 4-month phase. Because the study could not be blinded, bias in the adjustment of insulin doses remains a possibility. However, the data on insulin levels and nocturnal glycemia patterns allay these fears because both treatment arms appear reasonably optimized for safety and morning glycemic control.

Other strategies to reduce the incidence of nocturnal hypoglycemia do exist. The incidence of nocturnal hypoglycemia is decreased by 70% when insulin lispro is used instead of regular insulin in the setting of intensive insulin therapy (11). Moreover, although continuous subcutaneous insulin therapy can reduce the occurrence of hypoglycemia (12) in general and can improve hypoglycemic awareness (13), data on the reduction of nocturnal hypoglycemia are lacking.

There is hope that glargine, a recently introduced long-acting insulin analogue that provides nearly peakless serum insulin levels over many hours, may reduce the risk for nocturnal hypoglycemia. Several clinical trials comparing glargine with neutral protamine Hagedorn (NPH) insulin, all in the setting of intensive glycemic goals for type 1 diabetes mellitus, have shown variable results. One 4-week study (14) found a small increase in the prevalence of nocturnal hypoglycemia with glargine; meanwhile, another 4-week study (15) found a decrease when only the final week was considered. A 16-week study (16) found no difference in nocturnal hypoglycemia rates between glargine and NPH insulin, although the rate of nocturnal hypoglycemia was higher with glargine during a 4-week titration period. Finally, a 28-week study (17) found a 36% reduction in rates of nocturnal hypoglycemia with use of glargine. Most of these studies found lower fasting blood glucose levels in the glargine groups (14–17), and all found slightly lower or similar hemoglobin A_{1c} levels. Taken together, these studies appear to show that glargine, when administered at bedtime, may reduce the risk for nocturnal hypoglycemia without a decrement in glycemic control; however, the risk for nocturnal hypoglycemia may initially increase during the first weeks of treatment.

Young children with diabetes are at high risk for nocturnal hypoglycemia, with single-night prevalence rates of 18% to 47% (7–9). This is especially concerning given that recurrent hypoglycemia in this age group has been associated with developmental and cognitive impairment (18, 19). However, because intensive insulin therapy remains unstudied and controversial in this age group, many young children with diabetes receive mixed-insulin regimens. Would it be safer in this group, even in the context of nonintensive glucose goals, to use a split-insulin regimen? This question remains untested.

Although the reduction in the rate of nocturnal hypoglycemia with administration of bedtime versus predinner NPH insulin is important, Fanelli and colleagues describe patients who had successfully achieved target hemoglobin A_{1c} values of 6.7% even before randomization. This alone is remarkable. The intensively treated group in the Diabetes Control and Complications Trial had achieved a mean value of only 7.2%. So, what is particularly different about Fanelli and colleagues' patients or about the approach to treatment that provided for such successful glycemic outcomes? Although multiple daily injections with evening split-insulin administration are fairly standard in the pediatric population, we have a long way to go to achieve these goals safely, effectively, and consistently (20).

The choice of an insulin regimen for a person with diabetes mellitus is an individual process that balances factors such as the desired level of control, hypoglycemic awareness, daily routines, meal habits, and scheduled daily health tasks. A fundamental tenet of medicine is that medication regimens requiring fewer daily administrations are superior to those requiring more administrations, given equal efficacy. An additional injection per day is not a trivial one. We in the medical community must continue to search for the safest possible means of achieving optimal glycemic control in our patients so as to derive the lowest possible risk for long-term complications. Evidence now suggests that for a selected group of persons with type 1 diabetes mellitus, an extra shot at bedtime should be considered, although newer insulin analogues may yield additional approaches and benefits in the near future.

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C-Reactive Protein Risk Prediction: Low Specificity, High Sensitivity

Convincing evidence indicates that both local inflammation in the arterial wall and systemic signs of inflammation are important in atherogenesis and in complications of atherosclerotic disease. Consistent results from more than 15 well-conducted prospective studies in initially healthy persons (1) have shown a strong and independent association between the circulating concentration of C-reactive protein (CRP)—the classic acute-phase reactant, measured by high-sensitivity assays—and cardiovascular end points, including acute myocardial infarction, stroke, and progression of peripheral arterial occlusive disease. This strong association is seen for both primary and secondary prevention (patients with manifest atherosclerotic disease). Increased CRP levels predict recurrent instability in patients admitted with an acute coronary syndrome; in patients undergoing invasive procedures, such as percutaneous transluminal coronary angioplasty, stenting, or bypass grafting; and in other high-risk groups, such as patients with renal insufficiency and those who have had transplantation. Thus, CRP is itself an important general marker of increased risk for cardiovascular events, including death, and has also been shown to add to risk prediction based on conventional risk factors (2). The latter observation is of considerable importance because about half of all new cardiovascular events occur in persons without classic risk factors.

However, it is critically important to recognize that CRP production—and systemic markers of inflammation and the acute-phase response, in general—is an entirely nonspecific reflection of a broad range of diverse pathologic processes (3, 4). This is in the sharpest possible contrast to the exquisite specificity of, for example, measurements of troponins as markers of myocardial damage in acute coronary syndromes. Increased values of CRP and other acute-phase reactants may reflect tissue damage and inflammation not only in the arteries but anywhere in the body; these elevated levels may be induced by metabolic, infective, immunologic, or other processes. Indeed, the triggers for the increased CRP production that predicts atherothrombotic events have not yet been identified. An intriguing possibility is that a significant component may not be abnormal inflammation or tissue damage at all, whether in the arteries or elsewhere, but hereditary or acquired hyperactivity or responsiveness of the cytokine cascade responsible for the acute-phase response (5, 6).

In this issue, Rifai and colleagues (7) present results from the Women's Health Study in which they compare the predictive value of CRP level for cancer and cardiovascular disease. Using a nested case–control design, the authors identified 643 women who developed cancer of various origins (58% breast and ovarian) or cardiovascular events and 643 women matched for age and smoking status who remained free of disease during 58-month follow-up. Baseline characteristics between patients developing cancer and the corresponding controls were similar, whereas women who developed a cardiovascular end point more frequently presented with risk factors and also had increased CRP levels. The main results showed a clear increase in incident cardiovascular events across increasing quartiles of CRP levels: The adjusted relative risk was 5.6 if the top quartile was compared with the bottom quartile; however, the 95% CI was somewhat large (2.3 to 13.2). In contrast, no such association was seen with incident cancer (relative risk in the top quartile vs. the bottom quartile, 1.2 [CI, 0.9 to 1.6]). The authors conclude that CRP level appeared to independently predict cardiovascular disease but not cancer in their study sample of middle-aged low-risk women.

Rifai and colleagues' conclusion clearly seems justified on the basis of the data presented. However, the authors go one step further by asking in the title of their paper whether CRP may be specific for vascular disease in women. The short answer here is no, because the acute-phase response is essentially and inescapably a nonspecific response. C-reactive protein values can be interpreted only when there is full knowledge of the clinical state of the patient, as ascertained by a thorough physical examination and review of pertinent laboratory values. Any attempt to consider CRP level as specifically reflecting a particular abnormality would abolish the clinical value of this extremely informative, albeit nonspecific, analyte.

Although no previous study has analyzed the relationship between CRP level and incident cancer, several studies have examined the association between CRP level and all-cause mortality in middle-aged men (8) and women (9) and elderly patients of both sexes (10). In all these patient groups, baseline CRP level was positively and significantly related to total mortality, and the relative risks were similar for cardiovascular and noncardiovascular death. The one exception was the study by Mendall and colleagues (8), in which the association with total mortality remained significant only after multiple adjustments. In addition, several other markers of the acute-phase response—including leukocyte count (11, 12), interleukin-6 level (10, 13), plasma viscosity (14), fibrinogen level (15, 16), and albumin level (17)—have also been prospectively related to total mortality in large cohorts. In almost all the studies examining this relationship, the results were similar for cardiovascular and noncardiovascular deaths.

In this context, a recent large prospective study is of particular interest. In 3571 Japanese-American men 71 to 93 years of age participating in the Honolulu Heart Program (16), fibrinogen levels at baseline were associated with cause-specific mortality during 4.4 years of follow-up. In this sample, 728 participants died; cardiovascular disease caused 37% of these deaths, and cancer caused 27%. The relative risk for cause-specific mortality associated with a 1–standard deviation increase in fibrinogen level was 1.18 for cardiovascular deaths, 1.32 for cancer deaths, and 1.32 for other deaths. The consistent results of these studies relating markers of the acute phase to total mortality clearly underline the nonspecific nature of the acute-phase reaction in general, and CRP in particular, in the prediction of disease. This is further supported by two recent intriguing studies relating baseline CRP levels to incident type 2 diabetes mellitus (18, 19).

So, in light of these recent findings, how do we then interpret Rifai and colleagues' results? First, this data set provides valuable confirmation of earlier results from the Women's Health Study. Second, their results suggest that risk prediction for cardiovascular diseases in women may be less confounded by other conditions, such as malignancies, especially in middle-aged persons. However, although chronic inflammation may predispose patients to malignancy, this was not notably the case for the common types of cancer in women that were predominant among the participants in this sample. Moreover, although CRP levels at clinical presentation with several different tumors have been reported to predict clinical outcome, there is no previous evidence that an acute-phase response long precedes clinical presentation; however, the present study, by using high-sensitivity CRP measurements, confirms this.

In conclusion, the acute-phase response is an entirely nonspecific response to most forms of tissue damage, inflammation, and infection. The very modest acute-phase response detected most effectively by high-sensitivity CRP assay, as performed in Rifai and colleagues' study, may reflect abnormalities that lead to atherothrombotic events or may reflect metabolic factors related to increased cardiovascular risk. Regardless of the underlying mechanisms, the empirical measurement of CRP is a powerful predictor of cardiovascular risk, as Rifai and colleagues elegantly reconfirm here. Furthermore, persistently increased CRP production is a sensitive and valuable nonspecific indicator of an ongoing disease process in the body that deserves serious and careful medical attention.

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EDITORIAL

Welcome, PIER, A New Physicians' Information and Education Resource

After more than 6 years of developmental effort and extensive user testing during the past 12 months, the American College of Physicians–American Society of Internal Medicine will unveil a preview version of PIER (Physicians' Information and Education Resource) at the 2002 Annual Session in Philadelphia. PIER is a central element in the College's ongoing efforts to provide high-quality educational and information tools for its members while embracing the new opportunities afforded by electronic media and the Internet.

PIER is an ambitious undertaking, similar in scope and importance to other respected College programs, such as its Medical Knowledge Self-Assessment Program (MKSAP) and its publication of evidence-based clinical practice guidelines through the Clinical Efficacy Assessment Program (CEAP). Under the editorial direction of Dr. David Goldmann, PIER has now produced about 130 peer-reviewed modules, each written by an authority and peer-reviewed by other experts. Each module addresses a common problem in internal medicine; many more are under development and will be added in the months ahead. The College will be evaluating PIER further in the coming months, and we encourage College members to explore PIER's capabilities by logging on to the College's Web site after the release of the preview version in April (http://pier.acponline.org). Your comments and suggestions will be extremely valuable to the developers as PIER continues to evolve. Eventually, the College will release PIER in a version for handheld computers and will work with vendors of electronic medical records and order-entry systems to integrate PIER into their products.

Edward H. Shortliffe, MD, PhD
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Regent, American College of Physicians–American Society of Internal Medicine

Currently, physicians do not pursue answers to most clinical questions even though we are surrounded by information (1). Although we highly value scientific advances and original research, we find that locating pertinent original research is difficult and time-consuming (2). We like reviews that synthesize large amounts of information (3), but we realize that many higher-quality systematic reviews address very focused clinical questions rather than a broad base of issues inherent to the management of complex patients. As a result, many of us look to textbooks because they are easy to use, give many answers quickly, and synthesize large amounts of different types of information (1, 3, 4). Unfortunately, traditional textbooks do not always reflect current state-of-the-art knowledge or extensively reference supporting evidence (5–7).

PIER (Physicians' Information and Education Resource), a new American College of Physicians–American Society of Internal Medicine information product, is now available to College members at http://pier.acponline.org/. PIER represents a new direction in medical publishing because it helps clinicians address complex, multifaceted questions in an informed manner. It is a Web-based information-support tool specifically designed to deliver rapidly accessible, comprehensive, up-to-date, and evidence-based guidance to clinicians. Written by experts and peer-reviewed, PIER presents information in a standard structure that mirrors questions and decisions that physicians routinely address when caring for patients.

We think of PIER as one of a new peerless breed of information resources that surpasses most current textbooks. Examples of this new breed include *Clinical Evidence* (www.evidence.org), *Scientific American Medicine* (www.samed.com), and *UpToDate* (www.uptodate.com). These resources blend the flexibility of electronic media with some of the rigor of systematic reviews and the readability of textbooks. What distinguishes this new breed of information resources from traditional sources of knowledge? First, they provide content in a layered manner that accommodates different types of use, such as quickly honing in on relevant management advice, browsing, or detailed reviewing. Second, some, including PIER, provide links and immediate access to a wide variety of resources, including the full text of original articles and important source documents, patient information material, and drug compendiums. Third, they are easy to use and have transparent "dummy-proof" mechanisms for locating material. Fourth, they are regularly updated with new evidence found by systematic surveys of the published literature. Fifth, the more rigorous examples, including PIER, use explicit methods to synthesize multiple bits of important information into palatable bites, separate the wheat from the chaff, and inform users about the quality of underlying evidence.

How does PIER differ from existing electronic information resources? PIER has unique comprehensive evidence-based content, and PIER delivers this content innovatively. Content is organized around five modules: Diseases; Screening and Prevention; Complementary and Alternative Medicine; Ethical and Legal Issues; and Procedures. The disease modules are modeled on the ways that seasoned clinicians think through cases. For example, sections address multiple aspects of medical care, including diagnosis, consultation, hospitalization, drug and nondrug therapy, patient education, and follow-up care. Each section has a few up-front, succinct evidence-based guidance statements for clinicians who are in a hurry. Clicking on a guidance statement brings up a specific recommendation and its supporting rationale, evidence, and comments. Recommendation statements have letter grades that alert physicians to the strength of supporting evidence, which may be drawn from multiple levels, such as randomized trials, observational studies, or expert opinion. Most important, PIER is easy to navigate. The individual clinician can move quickly through PIER—from general management principles to specific recommendations to supporting evidence to source bibliographic material to related drug reference material and to a host of other linked material—and can tailor his or her use of PIER to meet varied and particular needs.

Improvements in access to and dissemination of medical knowledge afforded by electronic products, such as PIER, are a needed and welcome addition for medical practice. Even better is yet to come. Editors and authors of these products will refine their skills in managing tradeoffs between more frequent updating, broader topical coverage, and more rigorous reviewing methods. They will "grow" their products by continually adding more chapters and new content. Researchers will learn more effective ways of synthesizing and structuring information so that it meets clinicians' needs and allows for varied learning styles. A single format, such as the long, unstructured chapters of current print textbooks, will be a thing of the past. We will have to adapt to new formats containing rich mixtures of print, audio, and visual material. Technological advances with handheld devices will allow better delivery of content. Common computer language protocols will allow us to integrate electronic information sources such as PIER with electronic medical records and expert diagnostic systems. These integrated systems will make it easier for physicians to make the link between a patient's medical problem and the pertinent medical knowledge. Ultimately, we will see more ideal clinical information systems, similar to those advocated by Haynes, whereby clinicians and patients always have the benefit of current best evidence (8).

Welcome, PIER, and thank you for taking us one more step toward this bright vision of the future.

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LETTERS

Helicobacter pylori Eradication Therapy for Nonulcer Dyspepsia

TO THE EDITOR: We were interested to read the systematic review by Laine and colleagues (1) suggesting that *Helicobacter pylori* eradication therapy was not effective in nonulcer dyspepsia. We previously published a systematic review within the Cochrane Collaboration that reached a different conclusion (2), namely, that *H. pylori* eradication was associated with an increase in cure of symptoms in nonulcer dyspepsia. The effect size we observed was modest (reduction in dyspepsia rate, 9% [95% CI, 5% to 14%]) but statistically significant ($P < 0.001$), and an economic analysis suggested that *H. pylori* eradication may be cost-effective in patients with nonulcer dyspepsia (3). This conclusion was maintained in all sensitivity analyses and did not depend on the results of any one trial.

We believe that our results differed from those of Laine and colleagues mainly because our review currently includes studies published up to May 2000 and Laine and colleagues curtailed their search in December 1999. Therefore, we included nine trials evaluating 2541 patients while Laine and colleagues included only seven trials and 1544 patients. In our analysis, we included abstracts only when authors provided further information, and we actually revised the results of one abstract (4). We summarized results by using risk ratios for continuing dyspepsia, while Laine and colleagues used odds ratios for cure (5). If Laine and colleagues had applied our methods, they would have found their results to be statistically significant.

Laine and colleagues reached their particular conclusion mainly because they had not included the most recent trials in their systematic review. The advantage of Cochrane systematic reviews is that they are continually updated, and time between submission and publication is short. This is particularly important in areas that are rapidly evolving, such as *H. pylori* eradication in nonulcer dyspepsia. There is now substantial evidence that *H. pylori* eradication has a beneficial effect on patients with this disorder.

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TO THE EDITOR: I am troubled by Laine and colleagues' conclusion that there is little support for the use of *H. pylori* eradication therapy in patients with nonulcer dyspepsia (1). Since infected persons have a two- to sixfold increased risk for gastric cancer and certain types of lymphoma, isn't it reasonable to therefore offer curative therapy? Do we really have longitudinal studies of sufficient duration to know the actual long-term risks associated with continued *H. pylori* infection? In the same issue, the findings of Ohkusa and associates that precancerous gastric lesions improved after eradication of *H. pylori* (2) certainly support the premise of long-term benefit.

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TO THE EDITOR: Laine and colleagues (1) have done an admirable job in analyzing published randomized, controlled trials of treatment of *H. pylori* in patients with nonulcer dyspepsia. They conclude that there is little support for eradication of *H. pylori* in dyspeptic patients (1). The study by McColl and coworkers (2), however, which was part of their meta-analysis, favors *H. pylori* eradication therapy and appears to be well designed and well executed. Although there are some methodologic differences between this trial and the three other large studies reported by Laine and colleagues, they do not appear to be enough to explain the disparity in results.

One other difference between the McColl study and the other studies is that metronidazole was included in the treatment regimen. *Giardia lamblia* infection is prevalent in Scottish children, can be chronic, may not produce diarrhea, and would respond to metronidazole. One study found that 16% of Scottish children screened by the relatively insensitive technique of direct stool examination were positive for *Giardia* cysts (3). Treatment of giardiasis may account for a portion of the benefit described by McColl and coworkers.

Although the analysis by Laine and colleagues seems to lay the concept of *H. pylori* as the major cause of nonulcer dyspepsia to rest, I would echo the need for continued elucidation of the causes of this disorder and the need for better management options.

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IN RESPONSE: Meta-analysis involves more than calculating a summary estimate from an amalgamation of studies. The letter and meta-analysis of Drs. Moayyedi, Deeks, and Forman illustrate the need to assess other factors before drawing conclusions. The widely accepted definition of dyspepsia is upper abdominal pain or discomfort, excluding predominant reflux symptoms. Although Moayyedi and colleagues state that they excluded trials including participants with only reflux symptoms, the two positive trials in their meta-analysis included patients with reflux (1, 2). They report that a third trial was positive, but treatment success, the primary end point, did not improve with therapy (3). Analysis of studies in their review using the appropriate definition of dyspepsia shows no benefit ($P = 0.5$), just as in our meta-analysis.

Significant heterogeneity, as identified for our primary end point, suggests that studies may be too different to aggregate in a meta-analysis. Moayyedi and colleagues reported a P value of 0.53 for heterogeneity. However, using data from their meta-analysis, we calculated a P value of 0.15, which approaches statistical significance ($P < 0.1$). They state that removal of any article leads to similar results, but removal of a study leads to significant heterogeneity. In addition, Moayyedi and colleagues state that their conclusions were maintained in all sensitivity analyses, but they do not report any of their predefined sensitivity analyses. The sensitivity analysis they included had significant heterogeneity.

Application of Moayyedi and colleagues' methods to our meta-analysis (although not appropriate with heterogeneity) did not produce significance. Additional studies may alter results, but only one of their additional studies showed a significant benefit (8%. $P = 0.04$) (1). Although this study is more than twice the size of any other trial, it was not peer-reviewed, used a nine-symptom scoring system that includes nondyspepsia symptoms, and has uncertain methods. The other additional studies had differences of −4% to 2%, similar to those in recently published large studies showing no benefit (4).

Ultimately, meta-analysis requires an appropriate examination of study design and patient population. Primary summary estimates from our meta-analysis and the meta-analysis by Moayyedi and colleagues are similar. However, more careful evaluation of both meta-analyses shows no suggestion of benefit when appropriate definitions of dyspepsia are used or when dyspepsia scores are analyzed. Without critical analysis of studies, a larger meta-analysis does not produce a more credible meta-analysis.

Dr. Buckingham suggests screening for *H. pylori* to prevent gastric cancer. An association of cancer with lifelong *H. pylori* infection cannot be taken as evidence that eradication decreases cancer risk, and no randomized trial has demonstrated such a benefit. The lack of documented benefit and the high cost (estimated at $1 billion [5]) prevent our recommending widespread screening for *H. pylori* infection.

Dr. Bozdech raises an intriguing idea, although we know of no documentation showing that giardiasis accounts for a substantial proportion of cases of nonulcer dyspepsia.

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Acute Exacerbations of Chronic Obstructive Pulmonary Disease

TO THE EDITOR: I read the position paper on acute exacerbations of chronic obstructive pulmonary disease (COPD) with great interest (1, 2). The statement that mucolytic medications are not beneficial needs further comment. The authors failed to mention a Cochrane review that primarily discussed the preventive effect of mucolytic agents on exacerbations but also showed that mucolytic therapy was associated with a significant reduction in days of disability (0.65 day per patient per month) and days of treatment with antibiotics (0.68 day per patient per month) (3). Furthermore, the authors did not consider *N*-acetylcysteine, which is a thiol-containing substance that may act as an anti-inflammatory drug. In our systematic review of randomized, controlled trials of *N*-acetylcysteine (4), my colleagues and I used a validated score to evaluate the quality of each study before including it in our analysis (5). Eleven of 39 retrieved trials were included, 9 of which addressed prevention of exacerbation and 5 of which addressed improvement of symptoms. With *N*-acetylcysteine, 61.4% of patients reported improved symptoms compared with 34.6% of patients receiving placebo (relative benefit, 1.78 [95% CI, 1.54 to 2.05]) (4). On the basis of the published data, the position paper's recommendations regarding mucolytics do not reflect the best available evidence.

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TO THE EDITOR: We read with interest the position paper reporting an evidence-based approach to the management of acute exacerbations of COPD (1). However, we disagree with the approach and the conclusions reached about antibiotic therapy. The authors stated that the available data support the use of antibiotics over placebo for acute exacerbations of chronic bronchitis, particularly if those exacerbations are severe. However, they also concluded that older, commonly used antibiotics, which would be ineffective against increasingly resistant strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, have not been proven to be any less effective than newer antibiotics and that newer antibiotics cannot be recommended in the absence of data from randomized trials. We believe that these statements do not adequately consider the available evidence supporting a role for newer, broad-spectrum agents in certain clinically complex patients who are especially likely to be infected with drug-resistant and other organisms not covered by narrow-spectrum agents. After reviewing a number of studies, we have concluded that 1) clinical features (age, lung function, frequency of exacerbations and antibiotic use, presence of other illnesses, use of corticosteroids, and need for home oxygen) can be used to define patients who are particularly likely to harbor drug-resistant organisms (2, 3); 2) newer, broad-spectrum agents do have an outcome benefit (fewer hospitalizations and longer time between exacerbations) compared with older antimicrobials (4, 5); and 3) the "cost of failure" with older agents may be great in patients with severe underlying lung disease, resulting in hospitalization and even mechanical ventilation. We agree that randomized, controlled trials comparing older and newer antibiotics are required. However, we consider it shortsighted to suggest that older antimicrobials are adequate therapy for all patients with acute exacerbations of chronic bronchitis and to recommend limited use of the newer and more active antimicrobials.

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IN RESPONSE: Dr. Stey rightly underscores the evidence for the role of the mucolytic agent *N*-acetylcysteine in the outpatient management of *stable* COPD and in prevention of acute exacerbations of COPD. However, our review focused on the management of acute exacerbations in the emergency department and in the hospital setting. Preventive measures and management of stable COPD were excluded from the review because they did not pertain to our specific research question. Drs. Niederman, Sethi, and Martinez favor the use of newer, broad-spectrum agents in the management of severe acute exacerbations of COPD. They base their recommendation on their view that such exacerbations are bacterial in origin (1), on the increasing rates of antibiotic resistance, and on studies that were excluded from our review because of methodologic flaws (retrospective design and no stratification for disease severity [2]; open-label design and a control group that included the use of broad-spectrum antibiotics [3]). The reasoning behind our recommendation is as follows. First, it is not clear that all acute exacerbations of COPD have a bacterial cause (4). Second, antibiotic trials in acute exacerbations of COPD have shown no benefit or small benefit for severe exacerbations. These trials are often criticized because they are mostly from the 1960s and 1970s and used "old" narrow-spectrum antibiotics. It is argued that with today's rates of antibiotic resistance, particularly in *Streptococcus pneumoniae* and *Haemophilus influenzae*, these trials do not reflect the current practice environment. However, although at the time of those trials the bacteria were generally sensitive to narrow-spectrum agents, only a small benefit was seen in patients with more severe exacerbations (5). We agree that patients with COPD are at higher risk for carrying resistant bacteria, depending on the frequency of hospitalizations and on disease severity, but there is currently no evidence to support the use of broad-spectrum antibiotics over narrow-spectrum ones. Thus, as frequently happens, we have come to a different conclusion when interpreting the evidence. We maintain that the increase in antibiotic-resistant organisms emphasizes the need to restrict the use of antibiotics to agents with proven efficacy in cases where they will make a significant difference in outcome. We assert that there is currently insufficient evidence to justify the use of broad-spectrum agents in acute exacerbations of COPD. Our hope is that these guidelines will decrease the unnecessary use of broad-spectrum antibiotics and stimulate further research comparing older and newer agents.

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Laser Removal of Radiation Tattoos

TO THE EDITOR: We have noticed, with some bafflement, a reluctance among oncologists to refer patients for removal of positional tattoos placed to facilitate radiation therapy. Perhaps oncologists view this as a trivial concern compared with the cancer treatment itself, or perhaps they believe that the tattoos do not bother patients.

In our experience, positional tattoos, especially those in cosmetically sensitive locations such as the presternal area and the breast, may contribute substantially to the dehumanization of patients grappling with a malignancy. When there is a hiatus in treatment or a prolonged remission, removal of the tattoos can be a liberating, hopeful experience. Patients understand that the tattoos are not dangerous, but they nonetheless appreciate the small kindness of physicians who offer to treat them (1, 2). Erasure of the visible stigmata of the cancer can be a milestone in the process of emotional recovery.

Highly effective means are now available for the removal of tattoos (3–5). The current generation of Q-switched lasers (for example, ruby, alexandrite, or neodymium–yttrium aluminum garnet) destroy tattoo pigment without inducing cutaneous scarring. Extremely brief, nanosecond-domain pulses prevent residual thermal damage from injuring the normal skin around the target sites. Blue-black inks used in radiation tattoos are particularly amenable to laser treatment; unlike complex, multicolored pictorial tattoos, radiation tattoos can typically be completely removed after one or a few treatments, each lasting seconds to minutes. No anesthesia is required, and any skilled laser surgeon can perform the outpatient procedure. Reimbursement is seldom an issue; few insurance companies will argue that removal of radiation tattoos is a cosmetic intervention. In addition, cutaneous laser specialists are often happy to be of service. If interested oncologists or internists are unaware of an appropriate referral center in their area, they may contact the American Society for Laser Medicine and Surgery.

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MEDICAL WRITINGS

Putting Ethics into the Medical Record

The medical record is a sensitive indicator of how care is administered, reflecting not only the structure of clinical thinking but also the values embedded in medical practice. Ostensibly, the medical record identifies all the existing clinical issues, assesses each individually, and then integrates these issues to ensure that the patient receives thorough care. But the aspiration toward integrated, comprehensive health care remains, and the medical chart continues to be piecemeal and, more telling perhaps, incomplete—clearly revealing lingering frustrations facing patients and their health care providers. Physicians are in the midst of a self-conscious reappraisal of how care can be administered more effectively and, at the same time, with more empathy (1, 2). From this perspective, I offer my proposal.

Consider an addition to the medical record—one that heretofore was implicitly present but now must be made explicit: Insert a section called *Ethical Concerns.* It will be integrated into the medical chart, starting with the admission note and then the progress notes and, finally, the discharge summary. *Ethical,* in this context, refers to the deliberations concerning all matters related to the value-based decisions that are constantly made when caring for a patient. Broadly speaking, value judgments inform and guide implementation of knowledge. The scientific and technological tools of clinical medicine are applied in a context of complex personal and social factors. In short, medical decisions are made and implemented in a "moral space" of patient values. Thus, beyond the exercise of their knowledge of clinical science, physicians must draw on their empathy and moral understanding to address the myriad challenges that arise in the exercise of effective care. These matters, as crucial as they might be, are rarely voiced in the medical record and thus remain conspicuously muted.

THE MEDICAL RECORD: A REFLECTION OF VALUES

In an Ethical Concerns section of the medical record, a synthesis of personal, social, and moral issues related to patient care would expressly address these complex matters. Here, physicians would address problems ranging from decision making in crisis to the mundane details of support for patients during the hospital stay and after discharge. I maintain that only by making deliberate efforts to identify such questions does the physician effectively address the concerns that are often closest to the patient's own experience of illness. Most physicians believe that they function with moral sensitivity, but, clearly, some are more naturally attuned to moral concerns. Here, I propose that an entrance be provided into a domain that has hitherto remained obscured by the vapors of good intentions. Constructing such a portal will require a reorientation, or better, an expansion of the assembly of all the components of the clinical case. More than a scientific and legal document, the medical record might then become a more comprehensive construction of a person's illness.

The medical record can be seen as a type of narrative (3): It tells a story of disease. The contents of that story formulate, structure, and thereby interpret. With its emphasis on clinical problems, the medical record exposes an ethos, revealing both the accepted mode of care and the logic underlying practice. The structure of record keeping reflects and may even determine the kind of care given. When the moral concerns of the patient are specifically addressed as part of the medical encounter, a formal means for considering these matters is established. This is a simple, yet crucial, revision of current medical record keeping. When the busy physician is required to attend to this dimension of patient care, the empathy assumed to be embedded in the character of the caregiver is reinforced, and concerns of the ill that are too often bypassed or forgotten are explicitly emphasized.

IMPLEMENTATION

What might an "ethical work-up" section of the medical record entail? Where should it appear? Should a series of specific questions be asked or a prescribed format followed? What are the limits of such an inquiry or, more clearly, how comprehensive should the attempt to address such concerns be? Clearly, different patients have different requirements, and different questions dominate different clinical settings. Whatever the specific characteristics of a given case, a conscious effort must be made to consider the patient's values. No less important, physicians must understand the values that

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Table 1. **Fourfold Ethics Evaluation***

1. Medical indications: Define clinical problems, goals of treatment, probabilities of success, and plans for care if therapy fails; delineate cost–benefit ratios of care.
2. Patient preferences: Maintain patient's right to choose by determining preferences for care; assess patient's competence and ability to adhere to medical treatment; if incompetent, is there health care proxy or advance directives?
3. Quality of life: Specify prospects, with or without treatment, of patient's recovery; define physical, mental, and social consequences of treatment success; and explore plans for care if treatment fails.
4. Contextual features: Clarify family or provider issues, including allocation of resources, financial constraints, and religious or cultural factors, that may influence clinical decisions; describe possible legal implications of treatment decisions (e.g., informed consent in clinical research or teaching settings); and establish the scope of confidentiality.

* Adapted with permission from Jonsen et al. (9).

guide their own choices and actions. I offer no formula, but I do advocate an approach.

Defining the value structure of the patient and physician and making the structure explicit provide the basis by which the clinical encounter can be a consensual and cooperative effort. Because the moral space is constructed by a complex confluence of values, sometimes in perfect alignment and sometimes not, an ethical work-up must enunciate and, ultimately, encompass the values of the patient *and* the values of the clinician in the setting in which he or she operates. In other words, there is an ongoing negotiation as to what *can* be done and what *should* be done for each patient (4). I am advocating that we should make this deliberation explicit—that we should articulate the basic ethics that guide and inform clinical decision making.

In this formulation, the ethical examination is directed not only at the usual source of inquiry, the patient, but also at the physician. This is, perhaps, the most radical aspect of this proposal. Physicians have not been trained in self-reflection; in the scientific model, the medical gaze has been designed to be directed outward, to attain objectivity. It is crucial that physicians not only fully explain therapeutic options to their patients but also clearly delineate the ethical norms and meta-ethical assumptions (the basis on which one value is selected over another) that are the foundation of their medical opinions. To determine mutually agreed upon therapeutic goals, the physician must be aware that the decision is an adjudication of perspectives from which embedded values often silently determine what is seen, what is believed, and what is advised. The point of the exercise is to deliberately address potential conflicts of values *before* they arise and, as in any negotiation, to understand both points of view.

It is surprising that scant attention has been given to formulating a comprehensive "ethics work-up," although both general guidance (5) and specific protocols have been devised for certain problems, such as palliative care (6, 7). This is partially the result of competing systems of medical ethics (for example, axiomatic, consequentialist, consensual, or pragmatic ethics [8]), the sheer complexity of the issues involved, and the restrictions imposed by the specific characteristics of individual cases. Nevertheless, a fourfold practical approach (**Table 1**), which offers an orderly review of the ethical issues in any case, has been devised (9). **Table 2** outlines a deliberative procedure for determining a patient's moral profile and an ethical decision within this format (10). Implicit to this exercise is gathering facts, that is, obtaining clinical and psychosociologic data—a process that is already routine, or should be. The key modification lies in taking these facts and examining them not only in the accepted fashion (principally within the narrow pathophysiologic context) but also in the context of a coordinate system that includes both the values of the patient *and* the physician. Thus, the ethics work-up is directed toward understanding the patient's needs, resources, and values and then coordinating these elements with the physician's efforts, which are themselves directed by a set of personal and institutional values and priorities. The self-reflective elements of the ethics work-up make this portion of the clinical portrait fundamentally different from the rest of the chart, which is oriented from the perspective of the examining physician toward the patient. Here, a true dialogue is embraced.

Because the deliberation just described requires a comprehensive understanding of the case, I suggest that the Ethical Concerns section become the penultimate segment of the initial medical admission note, or first clinic encounter, placed just before the final Impression and Plan sections.

A likely question, given that medical practice already addresses the psychosocial setting of the patient's experience of illness, is why this modification in record keeping is required. Simply stated, the clinical priorities, as a function of the wider life concerns of the patient, are rarely described. Perfunctory notes about marital status and employment constitute an acceptable social history, and only ancillary narratives from psychiatrists or social workers provide a comprehensive picture of the patient in the home setting. I propose deliberately addressing this aspect of care by compelling physicians to define the moral space within which they administer care. If this is done, medical ethics will have a precisely defined place in the medical chart and will thereby powerfully direct and justify our mode of professional behavior.

Most cases require little or no ethical reflection (11). For those facing end-of-life decisions, resuscitation orders, living wills, autopsy requests, and health care proxies are already routine, and their enactment rarely presents an ethical problem in the sense of being unidentified. The dramatic settings of transplantation, in vitro fertilization, and abortion, for example, hardly need comment here, because the ethical concerns of such decision making are integral to these clinical encounters. The "extremes" of the medical spectrum are not my primary concern; my focus is the more ordinary cases in which the choices presented by the physician must take into account patient values that are not easily articulated and are often overlooked.

Medical ethics is not applied only in crisis management. In one report, almost one in seven patients had moral dilemmas that went unrecognized by the ward team (11). Although much depends on the population examined and the moral "index" adopted, I suspect further study will reveal this figure as conservative. Whatever the actual incidence, however, illness demands that extraordinary choices be made, and value-laden decisions require identification and deliberation. The physician has a crucial role to play in this determination.

There are compelling administrative rationales for recognizing ethical issues proactively (for example, obtaining resuscitation directives), but I am also advocating a certain ethos of caring to be integrated with the more typical clinical concerns of patient management. By emphasizing the legitimacy of moral deliberations, I seek another mechanism by which empathy is declared and exercised as a guiding principle of medicine. There is no available formula to address this humane dimension of care. To a large extent, empathy is, or should be, implicit in the character of all health care providers, and I would not dispute the essential good will of those who enter the healing professions. I do, however, seek a means to fortify the claims of empathy by embedding them in an increased sensitivity to moral concerns. In the harried climate of the busy clinic, a self-conscious effort to place such issues high on the agenda of care requires vigilant efforts. Simply put, physicians would benefit from support that stresses both empathy (a psychological attribute) and ethical reflection (a moral endeavor).

THE DEBATE

Physicians are expected to understand the multidimensional character of disease and the diverse cognitive and moral faculties required to be effective health care providers. While I appreciate that medical practice involves keeping a delicate balance between competing interests and the establishment of priorities, I believe a more sustained effort is necessary to maintain the humane elements in clinical care; to do so, deliberate efforts must be made. Those who regard this proposal negatively often argue along one of two lines. The first objection is related to economics, that is, the economics of time and professional priorities. According to this view, physicians are already overcommitted and do not have the resources to offer patients the requisite time to obtain the information called for here. The second objection is related to a deeper and thus more difficult

Table 2. **Presentation of Ethical Decision Making***

Step 1. Identify the significant human factors in the case: Demographics (e.g., age, occupation, education, family status, and home setting), behavior history (e.g., psychiatric profile, criminal record, and substance abuse), and religious and political attitudes relevant to health and medical care.

Step 2. Explicitly define value factors (medical, professional, and human) related to the patient, the health care professional, and other relevant persons involved in the case.

Step 3. Delineate all ethical choices and major value conflicts.

Step 4. Set priorities for conflicting values and give reasons for holding a position.

Step 5. Identify the criteria by which a decision is made, considering underlying ethical norms and meta-ethical assumptions (How was *this* decision, based on *that* value, moral?).

Step 6. Critique the assumptions underlying the decision made in step 5 and present the final opinion and strategy for dealing with the moral issues identified.

* Based on Thomasma (10).

issue: Although physicians may wish to be humane, they by and large function as technocrats and thus are rarely called on to exercise moral sensitivity. Consequently, the patient in the typical setting does not expect to discuss values and beliefs, and only in the most pressing circumstances do such deliberations take place. I sympathize with these complaints but believe that the naysayers should carefully consider my rejoinder.

As for the first concern, the economics of time and commitments divide the professional day by certain expectations and standards of conduct. If physicians were expected to devote more professional effort to getting to know their patients, the time required to accomplish this objective would be acknowledged as important and would be factored into daily practice. Denying priority to this issue not only provides telltale evidence of the problem but serves as an indictment of our health care system. Only by alerting both the professional and lay communities to the shortchanging that is obviously occurring can the medical profession begin to adopt formal standards that will eventuate in change.

But now the second objection looms menacingly before my proposal: Perhaps devoting more effort to establishing the moral relationship between physician and patient is unnecessary. Why should the physician move beyond serving as technocrat to serving as a more thorough caregiver? After all, is not medicine ultimately a scientific discipline, ever more beholden to technological applications? From this viewpoint, technical proficiency is paramount, and attention to humane values will come into play only as required and in a minimal expression. Others on the health care team—including nurses, social workers, clergy, and psychiatrists—can deal with ethical complications as they arise.

Here is the heart of the matter: From my perspective, medicine is fundamentally a moral commitment, that is, the care of the *person.* Science and technology serve that responsibility (12). *Patients* entrust their care to physicians, who exercise their medical skills to resolve a clinical problem. But *people* experiencing illness have a diseased body *and* a ruptured sense of selfhood. The patient knows little about disease but intimately experiences illness. Where is the boundary drawn between *patient* and *person*? As a scientific object, the boundary is quite evident; as a moral agent, there is no division. Indeed, the patient–person distinction exists as an ethical dilemma and testifies to a profound fragmentation. Failure to specifically address mending this divide ignores the complaints of those who rightly feel that their bodies may be adequately attended to but that their personhood is left to be rejoined catch-as-catch-can.

Medical ethics is more than judicial directives, risk management, and academic debate. It is the very foundation of medicine—the moral substrate on which clinical care is built (12). One might see most choices and actions, even the most mundane, as the enactment of some underlying value system, but such reflection is not ordinarily part of clinical praxis. In adopting serious measures to ensure that medical ethics does not become another subspecialty but rather flourishes as an integral part of every physician's training, conduct, and practice, the profession must embed moral self-awareness in the medical record and thereby make moral deliberation explicit and routine. To that end, including an Ethical Concerns section of the medical chart that specifically addresses how well the physician has recognized the patient's experience of illness and incorporated that perspective in decision making is another step in improving efforts to ensure empathetic and ethical care.

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Ann Intern Med. 2002;136:559-563.

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AD LIBITUM

Palpation

It's not my fingers haven't told me
truths about a summer honeydew,

the underside of leaves
and warmth retained in the evening's lake.

It's not they wouldn't understand
the need to move like whispering

beneath my daughter's hair,
around my husband's mouth.

But when I make them probe
the complex privacy of my breast

invade its unresisting slide
across the mooring of my bones

my fingers are clumsy and reckless,
carnival seers foretelling my chances

of grief, romance, longevity,
declaring tragedy from mere abundance

or hurrying past some grain of truth
too hard to understand.

I'd rather let them gather into comfort
underneath this density of flesh, hold me

in suspense and tell the simpler story
of my weight and heat, passivity.

Nancy Fitz-Hugh Meneely
Chevy Chase, MD 20815

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MEDICAL WRITINGS

BOOK NOTES

Structured abstracts of information on newly published books, computer programs, selected Web sites, and other material are provided in this portion of Medical Writings. "Order phone" numbers can be used to place orders directly with publishers.

Provider-Patient Partnerships

Meldrum H, Hardy ML. 147 pages. Boston: Butterworth-Heinemann; 2001. $21.95. ISBN 0750673346. Order phone 781-904-2500.

Field of medicine: Clinician–patient interaction and communication skills.

Format: Softcover book.

Audience: Primary care physicians who desire to improve their ability to handle difficult situations and feelings that arise in ordinary patient encounters, especially in managed care settings.

Purpose: To provide a practical, case-based resource for interested physicians to improve their interactive skills.

Content: The first chapter presents a brief overview of essential interviewing skills. Subsequent chapters are topical, including setting limits, improving patient adherence, telling bad news, defusing anger, and dealing with other sensitive issues. Each chapter consists of two or more examples of difficult interactions in transcript format, followed by structured commentaries that indicate what went wrong in the interview and how the situation might have been handled differently. The book concludes with an eclectic summary chapter ("Things to Keep Thinking About").

Highlights: The case examples are the strongest feature of this book. The transcripts are lively, realistic, and sufficiently complex to sink your teeth into. The physician or "provider" demonstrates uneven skills, yet never sounds like an insensitive dunce. The authors' "how to" commentary is perceptive and often genuinely interesting.

Limitations: The caregiver in this text is always a "provider" and never a clinician. While I realize this economic jargon has become commonplace in medicine, it seems strange to use the "provider–consumer" model in a text devoted to empathy and negotiation. The book actually uses a mixed model—the patient remains a patient, but the physician becomes a provider—which may be a result of its understandable emphasis on managed care. Since this is not a text for beginners (that is, students and residents), it does not include a systematic approach to learning basic skills.

Related reading: Frederic W. Platt's *Conversation Failure* (Essential Science Publishing, 1992) and *Conversation Repair* (Little, Brown, 1995), each subtitled "Case Studies in Doctor-Patient Communication," offer a similar workshop-in-writing approach to improving one's interactive skills. In Platt's books, the cases are shorter, more numerous, and less complex, and the commentaries are wittier. *Provider-Patient Partnerships* complements and updates these earlier works. For a more learner-oriented textbook in the field of clinician–patient interaction, see *The Medical Interview: Mastering Skills for Clinical Practice*, 4th edition (FA Davis, 2001), by John L. Coulehan and Marian R. Block.

Reviewer: Jack Coulehan, MD, MPH, State University of New York at Stony Brook, Stony Brook, New York.

Exercise Prescription

Swan DP, Leutholtz BC. 188 pages. Champaign, IL: Human Kinetics; 2002. $22.00. ISBN 0736037543. Order phone 800-747-4457.

Field of medicine: Exercise physiology, sports medicine, and athletic training.

Format: Softcover book.

Audience: Physicians, physician assistants, nurse practitioners, and athletic trainers interested in a concise and current reference on how to advise and structure evidence-based exercise training regimens for patients with a variety of health and wellness concerns.

Purpose: To use case-study methods to aid students and exercise professionals in putting the American College of Sports Medicine (ACSM) exercise training recommendations into clinical practice.

Content: This well-organized text begins with an introduction of the case-study method. Subsequent chapters provide clear and well-written explanations of the principles of exercise training and the specifics of exercise prescription for cardiorespiratory fitness and muscular strength and flexibility. Many complex calculations are used in exercise physiology, and these are all broken down into easily understood components. This greatly facilitates the book's goal of making exercise prescription understandable to all readers. After the fundamentals are laid out, subsequent chapters deal with the specific clinical scenarios of exercise prescription for weight loss; for the older adult; and for persons with heart disease, diabetes, chronic obstructive pulmonary disease, pregnancy, and other conditions.

Highlights: The case-study method provides numerous useful examples that give the text a very hands-on feel.

Limitations: The authors are themselves experts in exercise physiology and exercise training. They point out areas where they may disagree with or feel more current evidence contradicts the ACSM guidelines. These discussions, while appropriate from an academic standpoint, distract from the primary purpose of the text as described above.

Related reading: *ACSM's Guidelines for Exercise Testing and Prescription*, 6th edition (Lippincott Williams & Wilkins, 2000), is a reference that all serious students of exercise physiology should own. For individuals interested in a comprehensive, current, in-depth, and easily read text on exercise physiology that expounds on the physiology introduced in this text, we recommend Cooper and Storer's *Exercise Testing and Interpretation* (Cambridge Univ Pr, 2001).

Reviewers: John F. Whitney, MD, and Gary H. Lyman, MD, MPH, Albany Medical College, Albany, New York.

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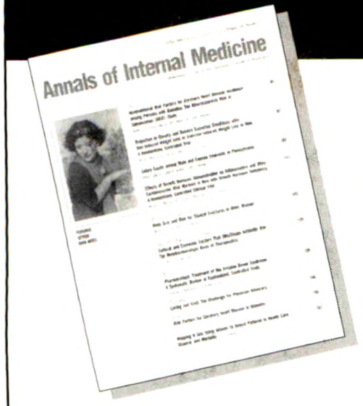

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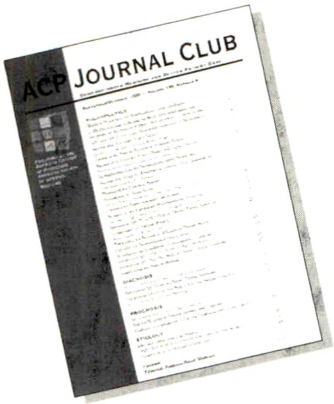

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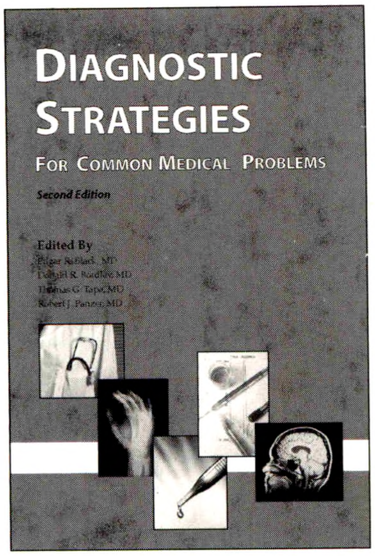

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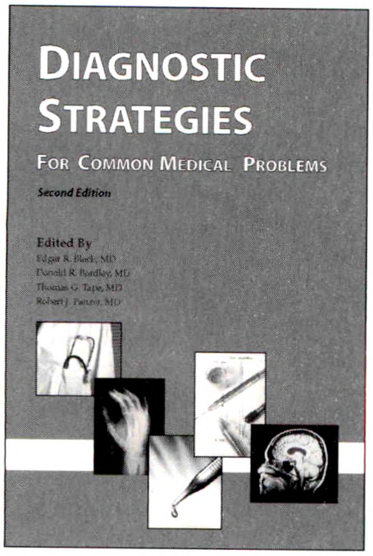

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J.B. Saaddine, M.M. Engelgau, G.L. Beckles, E.W. Gregg, T.J. Thompson, and K.M.V. Narayan

According to U.S. data collected from 1988 through 1995, a gap exists between recommended diabetes care and the care patients actually receive. These data offer a benchmark for monitoring changes in diabetes care.

Identification of Persons at High Risk for Type 2 Diabetes Mellitus: Do We Need the Oral Glucose Tolerance Test? 575

M.P. Stern, K. Williams, and S.M. Haffner

Persons at high risk for diabetes mellitus are better identified by using a simple prediction model than by relying exclusively on the results of a 2-hour oral glucose tolerance test. Although adding the 2-hour glucose variable to the model enhanced prediction, the resulting slight improvement entails greater cost and inconvenience.

High Risk for Hyperlipidemia and the Metabolic Syndrome after an Episode of Hypertriglyceridemia during 13-*cis* Retinoic Acid Therapy for Acne: A Pharmacogenetic Study 582

N. Rodondi, R. Darioli, A.-A. Ramelet, D. Hohl, V. Lenain, J. Perdrix, V. Wietlisbach, W.F. Riesen, T. Walther, L. Medinger, P. Nicod, B. Desvergne, and V. Mooser

Persons who develop hypertriglyceridemia during isotretinoin therapy for acne, as well as their parents, are at increased risk for future hyperlipidemia and the metabolic syndrome.

BRIEF COMMUNICATION

Severe Hepatotoxicity Associated with the Dietary Supplement LipoKinetix 590

J.T. Favreau, M.L. Ryu, G. Braunstein, G. Orshansky, S.S. Park, G.L. Coody, L.A. Love, and T.-L. Fong

Seven patients developed acute hepatotoxicity within 3 months of using LipoKinetix, a weight loss supplement. Despite extensive evaluations, no other cause for hepatotoxicity could be identified in these patients.

ACADEMIA AND CLINIC

Potential Physician Malpractice Liability Associated with Complementary and Integrative Medical Therapies 596

M.H. Cohen and D.M. Eisenberg

Physicians are increasingly grappling with medical liability issues as complementary and integrative health care practices are made available in conventional medical settings. This article proposes a framework in which physicians can assess potential malpractice liability issues in counseling patients about complementary and integrative therapies.

REVIEW

Chronic Renal Diseases: Renoprotective Benefits of Renin–Angiotensin System Inhibition 604

G. Remuzzi, P. Ruggenenti, and N. Perico

Certain renal diseases seen in clinical practice have a rapid course that soon causes irreversible end-stage renal failure caused by complete structural damage. These diseases, however, are rare. The more common nephropathies progress more slowly but still evolve to end-stage renal failure. A multimodal approach that centers on reducing or removing all risk factors associated with renal disease progression may decrease the time to remission for most patients with proteinuric nephropathies.

EDITORIAL

Balancing Safety of Dietary Supplements with the Free Market 616

J.D. Lewis and B.L. Strom

In this Issue, Favreau and colleagues report on cases of hepatotoxicity in users of the dietary supplement LipoKinetix. This and other recent reports of adverse outcomes associated with supplement use highlight two important issues that merit further consideration: 1) regulation and safety of dietary supplements and 2) safety surveillance.

Continued on page I-2

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CLINICAL GUIDELINE

The Role of High-Dose Chemotherapy and Stem-Cell Transplantation in Patients with Multiple Myeloma: A Practice Guideline of the Cancer Care Ontario Practice Guidelines Initiative 619

K. Imrie, R. Esmail, R.M. Meyer, and the Members of the Hematology Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative

The Hematology Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative has systematically reviewed the published literature and, through a consensus process, developed an evidence-based practice guideline assessing the role of stem-cell transplantation in patients with multiple myeloma. This paper discusses the six recommendations contained in the guideline.

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Cover photograph: Submitted by Charles Graver

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Dosing Guidelines for Adults

Fourth Edition

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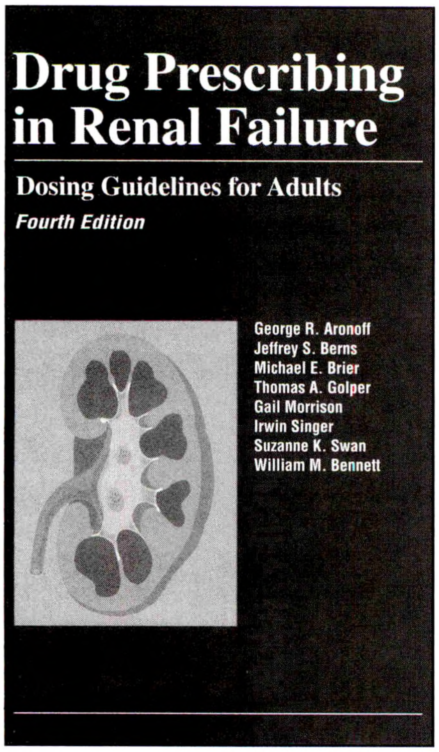

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Annals of Internal Medicine | ARTICLE

A Diabetes Report Card for the United States: Quality of Care in the 1990s

Jinan B. Saaddine, MD; Michael M. Engelgau, MD; Gloria L. Beckles, MD; Edward W. Gregg, PhD; Theodore J. Thompson, MS; and K.M. Venkat Narayan, MD

Background: Improving diabetes care in the United States is a topic of concern.

Objective: To document the quality of diabetes care during 1988–1995.

Design: National population-based cross-sectional surveys.

Setting: Third U.S. National Health and Nutrition Examination Survey (NHANES III) (1988–1994) and the Behavioral Risk Factors Surveillance System (BRFSS) (1995).

Participants: Participants in NHANES III ($n = 1026$) or BRFSS ($n = 3059$) who were 18 to 75 years of age and reported a physician diagnosis of diabetes. Women with gestational diabetes were excluded.

Measurements: Glycemic control, blood pressure, low-density lipoprotein (LDL) cholesterol level, biannual cholesterol monitoring, and annual foot and dilated eye examination, as defined by the Diabetes Quality Improvement Project.

Results: 18.0% of participants (95% CI, 15.7% to 22.3%) had poor glycemic control (hemoglobin A_{1c} level > 9.5%), and 65.7% (CI, 62.0% to 69.4%) had blood pressure less than 140/90 mm Hg. Cholesterol was monitored biannually in 85.3% (CI, 83.1% to 88.6%) of participants, but only 42.0% (CI, 34.9% to 49.1%) had LDL cholesterol levels less than 3.4 mmol/L (<130 mg/dL). During the previous year, 63.3% (CI, 59.6% to 67.0%) had a dilated eye examination and 54.8% (CI, 51.3% to 58.3%) had a foot examination. When researchers controlled for age, sex, ethnicity, education, health insurance, insulin use, and duration of diabetes, insured persons were more likely than uninsured persons to have a dilated eye examination (66.5% [CI, 62.6% to 70.4%]) vs. 43.2% [CI, 29.5% to 56.9%]) and were less likely to have a hemoglobin A_{1c} level greater than or equal to 9.5%. Persons taking insulin were more likely than those who were not to have annual dilated eye examination (72.2% [CI, 66.3% to 78.1%] vs. 57.6% [CI, 53.7% to 61.5%]) and foot examination (67.3% [CI, 61.4% to 73.2%] vs. 47.1% [CI, 43.2% to 51.0%]) but were also more likely to have poor glycemic control (24.2% [CI, 18.3% to 30.1%] vs. 15.5% [CI, 11.6% to 19.4%]).

Conclusions: According to U.S. data collected during 1988–1995, a gap exists between recommended diabetes care and the care patients actually receive. These data offer a benchmark for monitoring changes in diabetes care.

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For author affiliations, see end of text.

Diabetes, a typical example of chronic disease, currently affects 16 million people in the United States, causes considerable morbidity and mortality, and costs the nation almost $100 billion per year (1, 2). Fortunately, several efficacious treatment strategies to prevent or delay diabetes complications have emerged during the past decade, including control of glycemia, lipids, and hypertension; early detection and treatment of diabetic retinopathy, nephropathy, and foot disease; therapy with aspirin and angiotensin-converting enzyme inhibitors; and influenza and pneumococcal vaccines (3–12). Many of these treatments are cost-effective (13–17). However, their implementation in the United States remains suboptimal and varied (18–22). There is considerable pressure on U.S. health care systems to improve this situation and to deliver high-quality care while controlling costs. Influential bodies, such as the Institute of Medicine, have recently emphasized the need for strategies to improve the current quality of all medical care in the United States (23). Federal agencies are also increasingly responding with initiatives to address quality of care (24, 25).

One powerful quality initiative in the United States is the Diabetes Quality Improvement Project (DQIP), which is designed to influence the care of millions of U.S. patients with diabetes (26). The standard measures of quality of diabetes care proposed by DQIP were incorporated into the National Committee for Quality Assurance (NCQA) Health Plan Employer and Data Information Set. In contrast to guidelines or clinical goals for individual care, DQIP measures are designed to assess the performance of health care systems for a population, and they offer a way to make comparisons across health care systems. Several public and private health care systems, including the Indian Health Service (27), the Veterans Administration, the U.S. Department of

Context

There are no recent national evaluations of diabetes care in the United States.

Contribution

Using data from two national surveys, this study documents a substantial gap between the recommended and actual care of diabetes in the United States between 1988 and 1995. Many participants had hemoglobin A_{1c} levels greater than 9.5% (18.0%), poorly controlled blood pressure (34.3%), and elevated cholesterol levels (58.0%).

Implications

As a nation, the United States is falling short in caring for patients with diabetes. A periodic national "report card" may help us to gauge the success of future efforts to improve.

–The Editors

Defense, and numerous managed care organizations, have adopted these indicators.

Currently, there is no national reference for assessing the quality of diabetes care using a standard set of measures. Such a reference could help health care systems using DQIP measures to compare their own performance against population norms rather than the norms of other health systems. This reference could be a benchmark for assessing population changes in quality of diabetes care after implementation of national quality improvement initiatives recommended by the Institute of Medicine and NCQA. Furthermore, the use of a standard set of measures to assess the quality of diabetes care at a national level can facilitate international comparison. For this report, we used U.S. national data to provide a reference and benchmark of the quality of diabetes care as measured by the DQIP indicators.

METHODS

Surveys

We used two federally funded, nationally representative population-based surveys, the Third U.S. National Health and Nutrition Examination Survey (NHANES III) (1988–1994) and the Behavioral Risk Factors Surveillance System (BRFSS) (1995). Data from these two surveys were analyzed separately. Some measures came exclusively from NHANES III, and others came from BRFSS. We included adults 18 to 75 years of age who reported receiving a previous diagnosis of diabetes from a physician. Women with gestational diabetes were excluded. The two survey groups were similar in demographic characteristics, household income, health insurance coverage, and prevalence of diabetes. In NHANES III compared with BRFSS, more persons did not have a high school education (41.5% vs. 27.1%) and fewer persons used insulin (30.9% vs. 39.8%) (**Table 1**).

The methods for NHANES III are described elsewhere (28). Briefly, the NHANES III survey used a nationally representative sample of the civilian noninstitutionalized population obtained through a complex multistage cluster sampling design, with oversampling of non-Hispanic black persons, Mexican-American persons, and elderly persons. During a household interview, data were collected on sociodemographic characteristics and medical and family history. Within 4 weeks, this was followed by a clinical examination at a mobile examination center. The procedures for blood collection and processing have also been described elsewhere (29, 30). Low-density lipoprotein (LDL) cholesterol level was calculated by using the Friedwald equation for persons who fasted more than 8 hours ($n = 302$). Data from NHANES III were self-reported (demographic and clinical variables) or were obtained during clinical examination (hemoglobin A_{1c} level, cholesterol level, triglyceride level, and blood pressure). The survey included 16 705 participants 18 to 75 years of age, 1026 of whom reported receiving a diagnosis of diabetes from a physician before the survey.

The BRFSS is an annual random-digit telephone survey of state population–based samples of the civilian noninstitutionalized population of adults (≥18 years of age) in each of the 50 states and the District of Columbia. Its purpose, methods, and data analyses have been described in detail elsewhere (31). A diabetes-specific BRFSS module was used to collect data on clinical characteristics and preventive care practices from respondents with diabetes. Data from BRFSS were self-reported (dilated eye examination, lipid test, foot examination, and demographic and clinical variables). The survey included 103 929 participants 18 to 75 years of age, 3059 of whom completed the diabetes module and reported receiving a diagnosis of diabetes from a physician. We used the 1995 BRFSS so that the time frame would correspond with NHANES III.

Quality-of-Care Measures

We assessed the quality of diabetes care using indicators from the DQIP measurement set for which data were available. The DQIP began under the sponsorship of a coalition that included the American Diabetes Association, the Foundation for Accountability, the Health Care Financing Administration, and NCQA. The American Academy of Physicians, the American College of Physicians, the Veterans Administration, and the Centers for Disease Control and Prevention later joined the coalition. A committee of experts in diabetes care was responsible for developing the DQIP measure set. The DQIP classified the proposed indicators into three categories: accountability indicators, quality improvement indicators, and indicators under field-testing. The accountability measures, which are well grounded in evidence, have received consensus support from the scientific and medical community and have been extensively field-tested in a variety of health care settings. These measures are used to compare health systems and plans or providers. The quality improvement measures are not considered appropriate for comparing systems and plans or providers but were recommended by the NCQA for assessing internal performance. Table 2 shows all of the analyzed quality indicators and their data sources. The DQIP measures are a combination of process and outcome measures. In this paper, we use DQIP terminology and DQIP accountability and quality improvement measures.

Statistical Analysis

All analyses were conducted by using SAS software (SAS Institute, Inc., Cary, North Carolina) for data management and SUDAAN (Research Triangle Institute, Research Triangle Park, North Carolina) to account for the complex sampling scheme, the unequal probability of selection, the oversampling of certain demographic groups, and nonresponse factors (32, 33). Level of care was estimated by the percentage, with corresponding 95% CIs, of respondents who reported each preventive care practice. We estimated prevalence by groups of sex, age, ethnicity, education, health insurance, type of treatment, and duration of diabetes. Multiple logistic regression and computation of predictive margins were used to estimate the probability of receiving DQIP indicators when we controlled for all other independent variables. Predictive margins are a type of direct standardization in which the predicted values from the logistic regression models are averaged over the covariate distribution in the population (34). Predictive margins and their standard errors from logistic regression models are provided by the current version of SUDAAN (33). Taylor linearization is used in SUDAAN for calculating these standard errors. Odds ratios are usually used to display the result from logistic regression models. However, predictive margins are easier to interpret than odds ratios, and they do not require designating one of the groups as the referent group.

Table 1. **Characteristics of Persons with Self-Reported Diabetes in the Third U.S. National Health and Nutrition Examination Survey (1988–1994) and the Behavioral Risk Factors Surveillance System (1995)***

Characteristic	Persons in NHANES III (*n* = 1026) (95% CI)	Persons in BRFSS (*n* = 3059) (95% CI)
	%	
Age		
18–44 y	21.8 (16.7–26.9)	21.8 (18.3–25.3)
45–64 y	47.9 (42.6–53.2)	46.7 (43.2–50.2)
≥65 y	30.3 (26.4–34.2)	31.6 (28.7–34.5)
Female sex	54.0 (48.7–59.3)	55.3 (52.0–58.6)
Ethnicity		
Non-Hispanic white	71.5 (67.0–76.0)	69.4 (65.3–73.5)
Non-Hispanic black	16.0 (13.3–18.7)	15.6 (12.5–18.7)
Hispanic or Mexican American†	6.2 (5.2–7.2)	12.0 (8.3–15.7)
Other	6.4 (3.9–8.9)	3.0 (2.0–4.0)
Education		
<High school	41.5 (35.2–47.8)	27.1 (24.4–29.8)
High school	34.0 (28.7–39.3)	32.7 (29.8–35.6)
>High school	24.5 (18.4–30.6)	40.3 (36.6–44.0)
Married	64.7 (60.2–69.2)	63.5 (60.0–67.0)
Annual household income		
<$20 000	43.2 (37.3–49.1)	45.8 (42.3–49.3)
≥$20 000	56.8 (50.9–62.7)	54.2 (50.7–57.7)
Health insurance	91.6 (88.5–94.7)	87.6 (84.1–91.1)
Insulin user	30.9 (27.2–34.6)	39.8 (36.1–43.5)
Duration of insulin use		
0–5 y	38.0 (33.1–42.9)	30.4 (27.3–33.6)
5–14 y	40.2 (35.5–44.9)	39.0 (35.3–42.7)
≥15 y	21.8 (18.5–25.1)	30.6 (27.1–34.1)
Smoker		
Current	19.0 (14.1–23.9)	20.1 (16.6–23.6)
Former	41.7 (36.0–47.4)	34.2 (31.1–37.3)
Never	39.3 (34.6–44.0)	45.7 (42.2–49.2)

* BRFSS = Behavioral Risk Factors Surveillance System; NHANES III = Third U.S. National Health and Nutrition Examination Survey.

† NHANES III oversampled Mexican-American persons; BRFSS did not differentiate between Hispanic persons and Mexican-American persons.

Table 2. **Diabetes Quality Improvement Project Indicators and Related Data Sources***

DQIP Accountability Measure	DQIP Quality Improvement Measure	Data Sources
Percentage of patients receiving ≥1 hemoglobin A_{1c} test per year		BRFSS
Percentage of patients with hemoglobin $A_{1c} > 9.5\%$ (poor glycemic control)	Distribution of hemoglobin A_{1c} levels (7%, 7%–7.9%, 8%–8.9%, 9%–9.9%, ≥10%, none documented)	NHANES III
Percentage of patients assessed for nephropathy		Not available
Percentage of patients receiving lipid test once in 2 years		BRFSS
Percentage of patients with LDL cholesterol level < 3.4 mmol/L (<130 mg/dL)	Distribution of LDL cholesterol values (<2.6 mmol/L [<100 mg/dL], 2.6–3.3 mmol/L [100–129 mg/dL], 3.4–4.1 mmol/L [130–159 mg/dL], >4.1 mmol/L [>159 mg/dL], none documented)	NHANES III
Percentage of patients with blood pressure < 140/90 mm Hg	Distribution of blood pressure values (systolic, <140 mm Hg, 140–159 mm Hg, 160–179 mm Hg, 180–200 mm Hg, >200 mm Hg; diastolic, <90 mm Hg, 90–99 mm Hg, 100–119 mm Hg, >119 mm Hg; none documented)	NHANES III
Percentage of patients receiving dilated eye examination†	Proportions of patients receiving a well-documented foot examination	BRFSS

* All measures apply to patients between 18 and 75 years of age with type 1 or type 2 diabetes mellitus. Data were taken from each survey exclusively (the two surveys were not combined). BRFSS = Behavioral Risk Factors Surveillance System; DQIP = Diabetes Quality Improvement Project; LDL = low-density lipoprotein; NHANES III = Third U.S. National Health and Nutrition Examination Survey.

† Percentage receiving a dilated eye examination in the past year, or in the past 2 years if any two of the following conditions were met: not receiving insulin, hemoglobin A_{1c} level < 8.0%, no retinopathy in the previous examination. For our analysis, we used dilated eye examination in the past year as the quality-of-care measure.

RESULTS

Diabetes Quality Improvement Project Accountability and Quality Improvement Measures

Among adults 18 to 75 years of age with diabetes, 28.8% had had hemoglobin A_{1c} levels tested in the past year, and 18.0% had a hemoglobin A_{1c} level greater than 9.5%. Biannual lipid testing was done in 85.3% of participants, but only 42.0% had an LDL cholesterol level less than 3.4 mmol/L (<130 mg/dL). Only 65.7% had blood pressure less than 140/90 mm Hg, 63.3% had an annual dilated eye examination, and 54.8% had an annual foot examination (**Table 3**).

The distribution of the quality improvement measures (hemoglobin A_{1c} and LDL values and systolic and diastolic blood pressure) are shown in the **Figure**. The median hemoglobin A_{1c} level was 7.5% (CI, 7.2% to 7.9%). Less than half of the population (42.9%) had hemoglobin A_{1c} levels less than 7%, and 14.9% had hemoglobin A_{1c} levels greater than or equal to 10%. The median systolic blood pressure was 130.9 mm Hg (CI, 129.6 to 133.6 mm Hg). One fifth of participants had a systolic blood pressure of 140 to 159 mm Hg, and 9.1% had a systolic blood pressure of 160 to 179 mm Hg. The median LDL level was 3.5 mmol/L (CI, 3.4 to 3.8 mmol/L) (134.4 mg/dL [CI, 130.1 to 144.9 mg/dL]). More than half of the participants had an LDL level greater than 3.4 mmol/L (>130 mg/dL), and almost one fourth had an LDL level greater than 4.1 mmol/L (>160 mg/dL).

Regarding other preventive care measures, which may be considered as future quality indicators, only 45.7% of persons had received the influenza vaccine in the past year and only 26.5% had ever received the pneumococcal vaccine (**Table 3**). Only 38.0% monitored their blood glucose level at least once daily, and 58.0% had had a dental examination in the past year.

Factors Associated with Diabetes Care Measures

In unadjusted analysis, a higher proportion of persons at least 65 years of age received biannual lipid tests and annual dilated eye examinations compared with persons 18 to 44 years of age (88.9% vs. 74.0% [$P = 0.001$] and 70.2% vs. 50.4% [$P = 0.009$], respectively). Compared with non-Hispanic white persons, non-Hispanic black persons were more likely to have a hemoglobin A_{1c} level greater than 9.5% (29.9% vs. 15.7%; $P = 0.002$) and were less likely to have controlled blood pressure (<140/90 mm Hg) (56.7% vs. 66.3%; $P = 0.04$). Persons with education beyond high school were more likely to have controlled blood pressure than those who did not have a high school education (74.3% vs. 59.0%; $P = 0.06$). Insured persons were less likely than uninsured persons to have a hemoglobin A_{1c} level greater than 9.5% (17.5% vs. 34.8%; $P = 0.05$) and were more likely to have lipid tests and annual eye examinations (86.9% vs. 74.1% [$P = 0.008$] and 66.5% vs. 43.2% [$P = 0.006$], respectively). In the

BRFSS data, persons who did not see a physician because of cost (although they had health coverage) were less likely to have annual dilated eye examinations (46% vs. 67%; $P = 0.01$) and were less likely to have their cholesterol checked (76% vs. 87%; $P = 0.01$) compared with those who did not have cost considerations. Compared with nonusers, persons who used insulin were more likely to have a hemoglobin A_{1c} level greater than 9.5% (27.5% vs. 15.1%; $P = 0.002$) and to have received an annual dilated eye examination (72.2% vs. 57.6%; $P = 0.006$) and foot examination (67.3% vs. 47.1%; $P = 0.003$). Persons who used insulin were not as likely to have LDL levels less than 3.4 mmol/L (<130 mg/dL) (18.8% vs. 43.9%; $P = 0.07$) and were more likely to self-monitor blood glucose level at least once per day (60.3% vs. 23.4%; $P = 0.001$).

We obtained results after controlling for age, sex, ethnicity, education, health insurance, insulin use, and duration of diabetes (Table 4). Insured persons were more likely than uninsured persons to have had a dilated eye examination (66.5% vs. 43.2%; $P = 0.001$) and were less likely to have a hemoglobin A_{1c} level greater than 9.5% (17.7% vs. 26.9%; $P = 0.2$), although the latter difference did not reach statistical significance. Persons who used insulin were more likely than nonusers to have had an annual dilated eye examination (72.2% vs. 57.6%; $P = 0.001$ for the difference) and foot examination (67.3% vs. 47.1%; $P = 0.001$); however, those who used insulin were also more likely to have poor glycemic control (24.2% vs. 15.5%; $P = 0.02$). Persons 65 to 75 years of age were more likely than persons 18 to 44 years of age to have biannual lipid testing (90.6% vs. 71.9%; $P = 0.001$), annual dilated eye examination (69.7% vs. 53.4%; $P = 0.003$), and controlled blood pressure (48.1% vs. 93.1%; $P = 0.001$). Finally, non-Hispanic black persons were more likely than non-Hispanic white persons to have an elevated hemoglobin A_{1c} level (27.1% vs. 15.9%; $P = 0.002$) and poor blood pressure control (56.6% vs. 64.8%; $P = 0.08$).

DISCUSSION

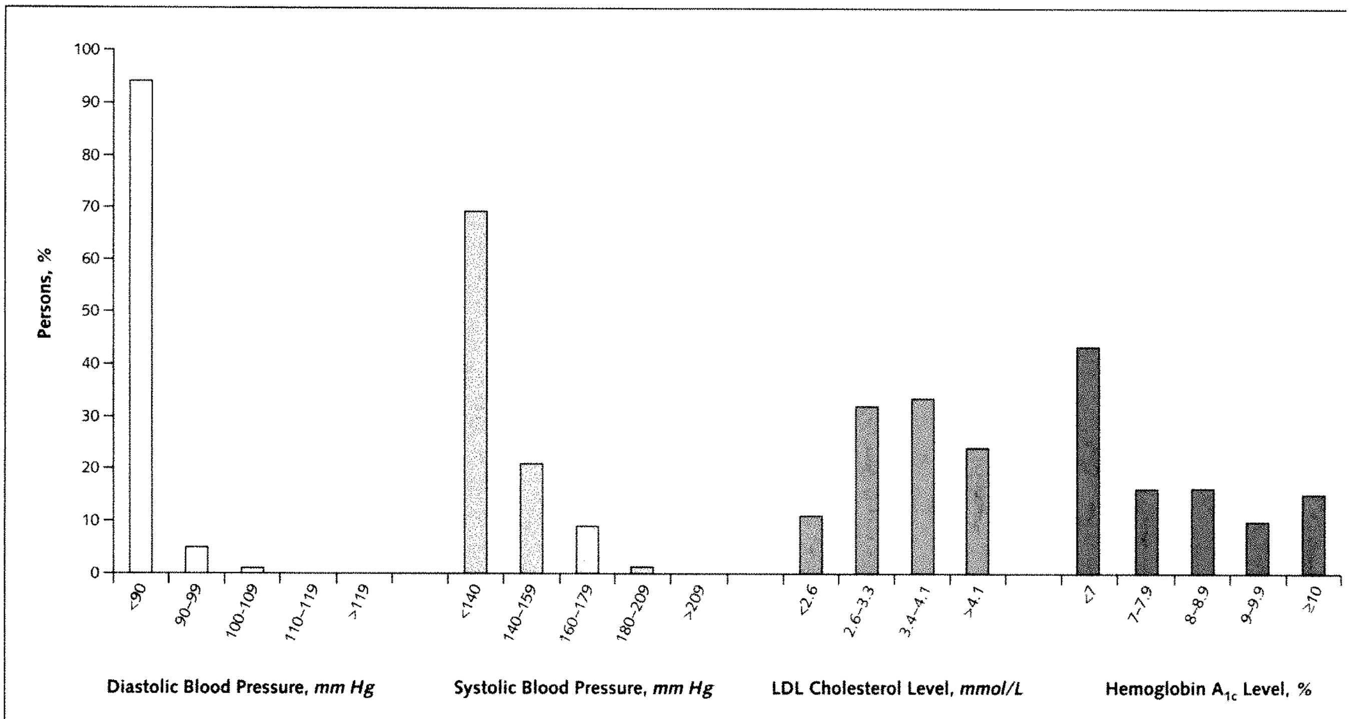
Using DQIP, a standard set of measures, we found that a large proportion of persons in the United States receives less than optimal diabetes care. Overall, 18.9% of participants had a hemoglobin A_{1c} level greater than 9.5%, 58.0% had poor lipid control, 34.3% had poor blood pressure control, 36.7% did not receive an annual dilated eye examination, and 45.2% did not have a foot examination. When applied to the estimated 7.9 million persons 18 to 75 years of age in the United States who have diagnosed diabetes, these statistics translated to an estimated 1.4 million persons with hemoglobin A_{1c} levels greater than 9.5%, 2.7 million with uncontrolled blood pressure, 2.9 million without annual dilated eye examinations, and 3.6 million without annual foot ex-

Table 3. **Persons 18 to 75 Years of Age with Diabetes in the Third U.S. National Health and Nutrition Examination Survey and the Behavioral Risk Factors Surveillance System Who Were Receiving Preventive Care***

DQIP Indicators	Patients (95% CI), %
Accountability measures	
≥1 test for hemoglobin A_{1c} per year	28.8 (25.1–32.5)
Hemoglobin A_{1c} level > 9.5%	18.0 (15.7–22.3)
Biannual lipid profile	85.3 (83.1–88.6)
LDL cholesterol level < 3.4 mmol/L (<130 mg/dL)	42.0 (34.9–49.1)
Blood pressure < 140/90 mm Hg	65.7 (62.0–69.4)
Annual dilated eye examination	63.3 (59.6–67.0)
Annual foot examination	54.8 (51.3–58.3)
Quality improvement measures	
Hemoglobin A_{1c} level	
<7.0%	42.9 (37.5–48.4)
7.0%–7.9%	15.7 (12.6–18.8)
8.0%–8.9%	16.4 (11.7–21.1)
9.0%–9.9%	10.0 (7.6–12.4)
≥10.0%	14.9 (11.6–18.2)
LDL cholesterol level	
<2.6 mmol/L (<100 mg/dL)	11.0 (5.9–16.1)
2.6–3.3 mmol/L (100–129 mg/dL)	31.1 (23.1–39.1)
3.4–4.1 mmol/L (130–159 mg/dL)	34.4 (26.0–42.8)
>4.2 mmol/L (>160 mg/dL)	23.6 (16.2–31.0)
Systolic blood pressure	
<140 mm Hg	68.5 (65.4–71.6)
140–159 mm Hg	21.1 (17.4–24.8)
160–179 mm Hg	9.1 (6.4–11.8)
180–209 mm Hg	1.3 (0.5–2.1)
>210 mm Hg	0.0
Diastolic blood pressure	
<90 mm Hg	93.5 (91.0–96.1)
90–99 mm Hg	5.5 (3.1–7.9)
100–109 mm Hg	0.9 (0.1–1.7)
110–119 mm Hg	0.1 (0.02–0.22)
>120 mm Hg	0.0
Other quality-of-care measures†	
Annual influenza vaccine	45.7 (42.4–47.0)
Pneumococcal vaccine	26.5 (23.2–29.8)
Self-monitoring blood glucose test (at least once daily)	38.0 (34.5–41.5)
Annual dental examination	58.0 (52.3–63.7)

* DQIP = Diabetes Quality Improvement Project; LDL = low-density lipoprotein.
† These measures are not currently part of the standard DQIP measures of care.

Figure. **Distribution of quality improvement measures in persons with diabetes.**



Data are taken from the Third U.S. National Health and Nutrition Examination Survey (NHANES III), 1988–1994. To convert mmol/L to mg/dL, divide by 0.0259. LDL = low-density lipoprotein.

aminations. Diabetes care in the United States can be vastly improved, and such improvement may yield substantial health benefits (35).

Clinical trials indicate that decreasing hemoglobin A_{1c} levels by 1 percentage point would reduce microvascular complications by 25% to 30% (3, 4) and that reducing blood pressure by 10 mm Hg would decrease macrovascular and microvascular complications and mortality rates by 35% (6). In addition, good lipid control can reduce the risk for coronary heart disease by 25% to 55% and the risk for death by 43% (8, 36). These results, together with our findings, suggest that improvement in quality of care can substantially improve the health of persons with diabetes nationwide.

Previous reports have indicated that quality of diabetes care in the United States is poor (18, 19, 22). Harris recently used a limited set of variables to describe the quality of national diabetes care (37, 38). Our study, which involved two large national data sets, adds to the existing literature through specific and comprehensive use of DQIP indicators to provide a practical benchmark for diabetes quality of care process and outcome indicators. Our study also provides a benchmark for quality of diabetes care in several important subgroups, such as age, sex, and health insurance status.

We found that receipt of preventive care varied consistently by two factors across groups. First, not having health insurance was highly associated with poorer status for several indicators. Previous reports have indicated marked ethnic differences in health insurance coverage and the risk for diabetes complications (39), and uninsured adults report greater unmet health needs than insured adults (40). Second, consistent with previous studies, insulin users in our study were more likely to receive preventive care (41, 42). This is probably because insulin use is linked to disease severity, and providers are more likely to follow recommendations when managing patients with severe disease. Although complications are more common among persons using insulin, the long-term risk for complications and the number of patients not taking insulin are both substantial. Health care providers and patients must better address preventive care if insulin is not used.

We found that non-Hispanic black persons had worse glycemic control than other ethnic groups; other reports also support this finding (43–45). Of interest, we found that non-Hispanic black persons did not differ significantly from participants from other ethnic groups in receipt of preventive services. Future health services research may need to identify reasons for poor glycemic and blood pressure control in black persons independent of access to care.

Several new measures (influenza vaccine, pneumococcal vaccine, self-monitoring blood glucose, and dental examination) may be considered for future national quality indicator sets. Many reports have demonstrated the efficacy of influenza vaccination among persons with diabetes. In a study by Nichol and colleagues, hospitalization decreased by 64% and respiratory disease decreased by 32% among vaccinated patients (46, 47). In our study, only 45% of participants had received the influenza vaccine. Reports have also demonstrated an association between diabetes and periodontal disease and missing teeth (48–51). These oral health problems can also complicate overall diabetes management and increase the risk for poor glycemic control (50). In our study, only 58% of persons with diabetes had visited a dentist in the past year.

Table 4. **Predictive Marginal Prevalence of Accountability Measures for Persons in the Third U.S. National Health and Nutrition Examination Survey and the Behavioral Risk Factors Surveillance System, according to Demographic and Clinical Variables***

Variable	Persons (95% CI)					
	Hemoglobin A_{1c} Level > 9.5% (n = 877)	Biannual Lipid Test (n = 2630)	LDL Cholesterol Level < 3.4 mmol/L (130 mg/dL) (n = 271)†	Blood Pressure < 140/90 mm Hg (n = 877)	Annual Dilated Eye Examination (n = 2630)	Annual Foot Examination (n = 2567)
	←——— % ———→					
Age						
18–44 y	23.5 (15.7–31.3)‡	71.9 (66.0–77.8)‡	33.5 (10.0–57.0)	93.1 (87.2–99.0)‡	53.4 (45.6–61.2)‡	52.7 (44.9–60.5)
45–64 y	19.1 (13.2–25.0)	87.7 (83.8–91.6)	40.8 (29.0–52.6)	61.7 (53.9–69.5)	64.4 (60.5–68.3)	56.3 (50.4–62.2)
65–75 y	14.5 (8.6–20.4)	90.6 (86.7–94.5)‡	36.9 (25.1–48.7)	48.1 (42.2–54.0)‡	69.7 (63.8–75.6)‡	56.2 (50.3–62.1)
Sex						
Male	16.1 (10.2–22.0)	83.2 (79.3–87.7)	44.0 (32.2–55.8)	66.4 (60.5–72.3)	60.3 (56.4–64.2)	56.9 (53.0–60.8)
Female	20.3 (14.4–26.2)	87.1 (85.1–89.1)	33.1 (23.3–42.9)	60.8 (54.9–66.7)	65.6 (61.9–69.3)	54.3 (48.4–60.2)
Ethnicity						
Non-Hispanic white	15.9 (12.0–19.8)‡	85.2 (83.7–87.7)	37.1 (29.3–44.9)	64.8 (58.9–70.7)‡	63.3 (59.4–67.2)	53.7 (49.8–57.6)
Non-Hispanic black	27.1 (21.2–33.0)‡	83.6 (77.7–89.5)	40.2 (24.5–55.9)	56.6 (48.8–64.4)‡	68.6 (60.8–76.4)	59.2 (49.4–69.0)
Hispanic or Mexican American§	22.2 (14.4–30.0)	85.6 (78.1–93.7)	53.7 (38.0–69.4)	64.1 (58.2–70.0)	60.7 (47.0–74.4)	60.7 (48.9–72.5)
Education						
<High school	20.4 (14.5–26.3)	81.0 (75.1–86.9)‡	37.1 (23.4–50.8)	61.6 (53.8–69.4)‡	58.5 (52.6–64.4)	52.3 (46.4–58.2)
High school	19.4 (11.6–27.2)	82.9 (79.0–86.6)	33.6 (16.0–51.2)	62.5 (54.7–70.3)	64.3 (58.4–70.2)	55.9 (50.0–61.8)
>High school	14.1 (6.3–21.9)	89.5 (85.6–93.4)‡	41.8 (20.2–63.4)	67.6 (59.8–75.4)‡	66.7 (60.8–72.6)	57.2 (51.3–63.1)
Health insurance						
Yes	17.7 (13.8–21.6)	86.3 (80.4–92.2)	39.4 (31.6–47.2)	63.5 (59.6–67.4)	66.5 (62.6–70.4)‡	55.8 (51.9–59.7)
No	26.9 (13.2–40.6)	80.7 (72.9–88.5)	22.5 (8.9–53.9)	60.8 (43.2–78.4)	43.2 (29.5–56.9)	53.1 (39.4–66.8)
Insulin use						
Yes	24.2 (18.3–30.1)‡	86.4 (82.5–90.3)	22.8 (3.2–42.4)‡	63.4 (55.6–71.2)	72.2 (66.3–78.1)‡	67.3 (61.4–73.2)‡
No	15.5 (11.6–19.4)	84.5 (80.6–88.4)	39.8 (32.0–47.6)	63.3 (57.4–69.2)	57.6 (53.7–61.5)	47.1 (43.2–51.0)
Duration of diabetes						
0–5 y	17.6 (11.7–23.5)	89.6 (85.7–93.5)‡	48.6 (34.9–62.3)	63.4 (53.6–73.2)	65.9 (60.0–71.8)‡	56.2 (50.3–62.1)
5–14 y	21.5 (13.7–29.3)	83.9 (80.0–87.8)	36.1 (24.3–47.9)	63.2 (57.3–69.1)	60.0 (54.1–65.9)	53.1 (47.2–59.2)
≥15 y	14.5 (8.6–20.4)	82.5 (76.6–88.4)‡	23.6 (7.9–39.3)	63.6 (53.8–73.4)	66.4 (60.5–72.3)	57.9 (52.0–63.8)

* Predictive marginal prevalence is interpreted as follows: If all persons in the population had had health insurance, the average of the predicted outcome of a hemoglobin A_{1c} level > 9.5% would be 16.6%. If all persons in the population had not had health insurance, the average of the predicted outcome of a hemoglobin A_{1c} level > 9.5% would be 34.8%. Values are averaged over the covariate distribution in the entire population for all variables other than health insurance and for independent variables (age, sex, ethnicity, education level, insulin use, and duration of diabetes) in the logistic regression model. Accountability measures for the Third U.S. National Health and Nutrition Examination Survey (NHANES III) were hemoglobin A_{1c} level > 9.5%, LDL cholesterol level < 3.4 mmol/L (<130 mg/dL), and blood pressure < 140/90 mm Hg; accountability measures for the Behavioral Risk Factors Surveillance System (BRFSS) were biannual lipid test, annual dilated eye examination, and annual foot examination. LDL = low-density lipoprotein.

† Includes persons who fasted and had a triglyceride level < 4.5 mmol/L (<400 mg/dL), for whom the Friedwald equation to calculate LDL cholesterol level was valid.

‡ $P < 0.05$ for the difference.

§ NHANES III oversampled Mexican-American persons; BRFSS did not differentiate between Hispanic persons and Mexican-American persons.

The DQIP indicators were initially developed for managed care organizations, which are becoming the main source of health care services for persons with diabetes in the United States. Even in 1990, 95% of health care benefits provided by U.S. employers involved some form of managed care (52, 53). Clearly, these indicators have considerable potential to accelerate the translation of research into clinical practice. Decisions to use specific values and distributions of hemoglobin A_{1c} levels, blood pressure, and LDL cholesterol levels as quality-of-care indicators represent a migration to measurement of intermediate outcomes. Such decisions are prompted by convincing research linking management of these indicators to reduced risk for microvascular and macrovascular complications of diabetes (3–7).

Our study has several limitations. Data were self-reported, which can result in recall bias. However, the BRFSS responses related to diabetes status and sociodemographic characteristics have a good to excellent reproducibility (54, 55) and validity (56). Reports have shown that the rates of a performance measure obtained from a member survey are usually higher than rates based on administrative data or abstracts of medical records (57). Even with this limitation, however, we still found suboptimal levels of care. Furthermore, we reported the distribution of hemoglobin A_{1c} level, blood pressure, and lipid levels based on examination and not on chart review. We used two different population-based surveys for this study, but sociodemographic characteristics and other important factors were similar in each. Practices have probably changed since these surveys were conducted in 1988–1994 and in 1995, but the extent of this change is unknown. This is especially important because many clinical trials, such as the Diabetes Control and Complication Trial and the United Kingdom Prospective Diabetes Study, released their findings in the late 1990s. The major value of our data is as a benchmark of the quality of diabetes care before the results of these major trials were released. Thus, the impact of national programs stimulated by these trials can be assessed.

Although health insurance was associated with several preventive measures, we could not explore the association further. The NHANES III and BRFSS surveys used similar yes/no questions to determine whether participants had health coverage, but they did not request more detailed information. In addition, neither survey assessed nephropathy status, self-management education, interpersonal care from provider, or participant satisfaction, all of which are important components of care that should be considered for inclusion in future national surveys.

Many U.S. adults with diabetes are receiving suboptimal care. We need to identify mechanisms at the patient, provider, and health care system levels to improve the quality of diabetes care (58). Health insurance was a strong correlate of several indicators, further supporting a large body of evidence indicating that more thorough coverage increases use of preventive care. Our data on the quality of diabetes care provide a national benchmark and can serve as a basis for focused clinical and public health efforts to reduce diabetes complications. These data also offer a normative set of the distribution of quality of care in the United States that will enable various organizations to compare and assess their own performances. When these methods are used, it may be possible to identify best care practices, and dissemination of these practices across settings could follow. When quality of diabetes care is described by using a standard set of measures, such as DQIP, future international comparison may be facilitated. It is clear from these data that a wide gap exists in the United States between our knowledge of effective diabetes interventions and their implementation in practice. This gap must be narrowed, and the recent emphasis placed on improving quality of care and translation research (23–25) is encouraging.

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Identification of Persons at High Risk for Type 2 Diabetes Mellitus: Do We Need the Oral Glucose Tolerance Test?

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Background: The standard method of identifying persons at high risk for type 2 diabetes mellitus involves detection of impaired glucose tolerance, which requires a costly and inconvenient 2-hour oral glucose tolerance test. Because clinical trials have indicated that diabetes is preventable by using behavioral or pharmacologic interventions, less expensive methods of identifying high-risk persons are needed.

Objective: To determine whether multivariable models are superior to glucose tolerance tests for identifying persons at high risk for diabetes mellitus.

Design: Prospective cohort study.

Setting: San Antonio, Texas.

Participants: 1791 Mexican Americans and 1112 non-Hispanic whites without diabetes at baseline who were randomly selected from census tracts.

Measurements: Medical history; body mass index; blood pressure; fasting and 2-hour plasma glucose levels; fasting serum total, low-density lipoprotein, and high-density lipoprotein cholesterol levels; and triglyceride level.

Results: For prediction of 7.5-year incidence of type 2 diabetes, the area under the receiver-operating characteristic (ROC) curve for a multivariable model involving readily available clinical variables was significantly ($P < 0.001$) greater than the area under the ROC curve for the 2-hour glucose value alone (84.3% vs. 77.5%). Impaired glucose tolerance represents a single point on the latter curve. Adding the 2-hour glucose measurement to the multivariable model increased the area under its ROC curve, but only from 84.3% to 85.7%.

Conclusion: Persons at high risk for diabetes mellitus are better identified by using a simple prediction model than by relying exclusively on the results of a 2-hour oral glucose tolerance test. Although adding the 2-hour glucose variable to the model enhanced prediction, the resulting slight improvement entails greater cost and inconvenience.

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In 1979, the National Diabetes Data Group defined an entity called impaired glucose tolerance, which reflects a degree of glucose tolerance that, although abnormal, is considered insufficient to merit a diagnosis of diabetes mellitus (1). This entity, which was later endorsed by the World Health Organization (WHO) (2, 3) and the American Diabetes Association (4), requires a 2-hour oral glucose tolerance test for its detection. It is important to emphasize that impaired glucose tolerance is by itself entirely asymptomatic and unassociated with any functional disability. Indeed, insulin secretion is typically greater in response to a mixed meal than in response to a pure glucose load (5); as a result, most persons with impaired glucose tolerance are rarely, if ever, hyperglycemic in their daily lives (5, 6), except when they undergo diagnostic glucose tolerance tests. Thus, the importance of impaired glucose tolerance resides exclusively in its ability to identify persons at increased risk for future disease.

The standard method for identifying persons at high risk for developing diabetes mellitus has been to identify persons with impaired glucose tolerance without regard to other diabetes risk factors. For example, nearly all of the clinical trials on prevention of type 2 diabetes have used impaired glucose tolerance as the principal enrollment criterion. Three of these trials—the Finnish Diabetes Prevention Study (7), the Diabetes Prevention Program (8), and the Study To Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) (9)—have recently reported positive results. Therefore, a need has arisen to identify persons at high risk for diabetes so that physicians can offer them preventive interventions. Because the 2-hour oral glucose tolerance test, which is necessary for the diagnosis of impaired glucose tolerance, is time consuming, costly, and inconvenient, it becomes relevant to ask whether other, more efficient means exist for identifying persons at high risk for diabetes.

A popular method of assessing the predictive discrimination of a test is to use a receiver-operating characteristic (ROC) curve (10) that plots the sensitivity of the test against the corresponding false-positive rate. In the present context, *sensitivity* refers to the percentage of persons whose initial values were above a given cut point

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Context

Lifestyle and pharmaceutical interventions can prevent overt diabetes in people with impaired glucose tolerance.

Oral glucose tolerance testing is the reference standard for identifying impaired glucose tolerance, but it is inconvenient and relatively expensive.

Contribution

The authors developed multivariable models that use readily available clinical variables to predict the development of diabetes.

The models were more accurate than oral glucose tolerance testing alone.

Adding results of oral glucose tolerance testing did not substantially improve the model's predictions.

Cautions

More than half the study sample was Mexican American.

Validation in other populations and translation for bedside calculation is needed before clinicians can use the model.

–The Editors

among all persons who later developed diabetes; *false-positive rate* refers to the percentage of persons whose initial values were above the cut point among persons who nevertheless remained free of diabetes. The area under the ROC curve is a measure of how well a continuous variable can predict the outcome of interest: If the sensitivity increases steeply as the threshold for diagnosis is relaxed, with only a relatively slow accumulation of false-positive results, the area under the ROC curve will be large; conversely, if the sensitivity increases slowly as the threshold for diagnosis is relaxed, with a rapid accumulation of false-positive results, the area under the ROC curve will be correspondingly smaller. The differences in the areas under two curves may be tested to see whether the apparent superiority of one continuous variable over another is statistically significant. We have used this approach to compare the 2-hour glucose value after an oral glucose load to various multivariable models for predicting future diabetes.

METHODS

Participants

Our analyses are based on data gathered in the San Antonio Heart Study. The methods of this study have been described elsewhere (11–13). Briefly, households were randomly sampled from three types of neighborhoods: low, middle, and high income. Residents of these households were eligible if they were 25 to 64 years of age and not pregnant. Because the number of non–Mexican-American persons residing in the low-income areas was negligible, only Mexican Americans were recruited from these neighborhoods. Stratified random sampling was used to recruit an approximately equal number of Mexican Americans and non-Hispanic whites from the middle-income and high-income neighborhoods.

The baseline data were collected in two phases, from 1979 to 1982 and from 1984 to 1988. A total of 5158 participants were enrolled in these two phases, representing a response rate of 65.3% of all eligible participants from the selected households. A follow-up examination was performed 7 to 8 years after the baseline examination on 3682 persons, representing 73.7% of the 4998 surviving study participants. The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved the protocol. All participants gave informed consent.

Measurements

Fasting plasma glucose levels were measured for all participants; they then drank a standardized 75-g glucose load (Koladex or Orangedex, Custom Laboratories, Baltimore, Maryland). The plasma glucose level was measured again 2 hours later. Although various protocols have been used for oral glucose tolerance testing, the glucose level obtained 2 hours after the administration of the oral glucose load is the only postload value that has been used as the basis for diagnostic categories (1–4); therefore, this was the only postload value that we considered. In line with common usage, we refer to this value as the 2-hour glucose value. Diabetes was diagnosed according to WHO criteria (fasting glucose level ≥ 7.0 mmol/L [≥126 mg/dL] or 2-hour glucose level ≥ 11.1 mmol/L [≥200 mg/dL]) (3). Persons who reported a history of diabetes diagnosed by a physician and who reported current use of insulin or an oral antidiabetic agent were considered to have diabetes regardless of their plasma glucose levels. Participants were asked to bring to the examination center a list of all prescription medications that they were receiving or the containers in which the medications had been dispensed. Participants who did not adhere to this request were subsequently contacted by telephone to verify their medications. Participants were classified as having diabetes if they met at least one of the above three criteria (fasting glucose value, 2-hour glucose value, or antidiabetic medications), even if all three variables were not recorded. Participants were classified as nondiabetic if all three variables were recorded and none met the criterion for diabetes. Persons with diabetes who were not taking insulin were considered to have type 2 diabetes. Participants with diabetes who used insulin were considered to have type 2 diabetes if they were at least 30 years of age at diabetes onset and if their body mass index (BMI) (weight in kg divided by height in meters squared) was greater than 27.0 kg/m^2. Nondiabetic persons were classified as having impaired glucose tolerance if their 2-hour plasma glucose level was 7.8 mmol/L or higher ($\geq$140 mg/dL) but less than 11.1 mmol/L (<200 mg/dL) (1–4). Height; weight; blood pressure; plasma glucose level; serum total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol levels; and serum triglyceride level were measured by using previously reported methods (11, 12).

Statistical Analysis

Baseline characteristics of the study sample according to sex and ethnicity were adjusted for age by analysis of covariance using SAS software (14). We developed a multiple logistic regression model with incident diabetes as the dependent variable and a panel of baseline characteristics that are ordinarily available in a routine clinical setting as independent variables. We refer to this model—which includes (with or without selected interactions, as explained in the Results section) age; sex; ethnicity; fasting and 2-hour glucose levels; systolic and diastolic blood pressures; total, LDL, and HDL cholesterol levels; triglyceride level; body mass index; and parental or sibling history of diabetes—as the *full model*. In addition to testing the statistical significance of each interaction term, we also used likelihood ratio tests to globally compare models with and without interactions. We assessed the importance of the 2-hour glucose value for predicting diabetes by comparing the full model with a nested model that excluded the 2-hour glucose value.

We also examined a simplified model based on widely recognized diabetes risk factors, which we call the *clinical model*. We believe that clinicians would more readily accept this simplified model because it entails fewer variables. The variables used in the clinical model were age, sex, ethnicity, fasting glucose level, systolic blood pressure, HDL cholesterol level, body mass index, and parental or sibling history of diabetes. This model was also examined with and without selected interactions and with and without 2-hour glucose value. We assessed the goodness of fit of all models by using the Hosmer–Lemeshow test (14).

We compared the predictive discrimination of the multivariable models to the predictive discrimination of the 2-hour glucose measurement by using ROC curves. The cutoff point defining impaired glucose tolerance represents only one of many possible cutoff points along the 2-hour glucose curve. The ROC curves were calculated for the multivariable models and for 2-hour glucose concentration by using SAS PROC LOGISTIC software (14), and were plotted for each 1% increment of the false-positive rate. The diabetes risks predicted for each person by the multivariable models were used in the analysis of the ROC curve. We used Stata software (15) to estimate the 95% CIs of the areas under the ROC curves and the statistical significance of differences between these areas according to the algorithm developed by DeLong and colleagues (16). We also compared nested models by using likelihood ratio testing. The 95% CIs of the areas under the ROC curves and the statistical significance of differences in the areas were then validated by use of the internal bootstrap resampling procedure (1000 samples with replacement) described by Harrell (17).

Role of the Funding Source

The funding source for this study, the National Heart, Lung, and Blood Institute, played no role in the design or conduct of the study or in the reporting of its results.

RESULTS

Of the 1838 Mexican Americans and 1166 non-Hispanic white persons without diabetes at the baseline examination, 208 Mexican Americans and 67 non-Hispanic whites developed type 2 diabetes in the 7.5-year follow-up period. Excluded from these tallies are 354 persons with diabetes at baseline, 192 whose diabetes status was indeterminate at baseline, and 132 whose di-

Table 1. **Age-Adjusted Diabetes Risk Factors at Baseline, according to Ethnicity and Sex, in the San Antonio Heart Study***

Variable	Mexican Americans		Non-Hispanic White Persons	
	Men (*n* = 732)	Women (*n* = 1059)	Men (*n* = 492)	Women (*n* = 620)
Age, *y*‡	42.6 ± 0.40	42.8 ± 0.33	44.6 ± 0.48	44.8 ± 0.43
Fasting blood glucose level, *mmol/L (mg/dL)*	5.0 ± 0.02 (90.1 ± 0.36)	4.8 ± 0.02 (87.2 ± 0.30)	5.0 ± 0.02 (89.6 ± 0.44)	4.8 ± 0.02 (86.2 ± 0.39)
2-Hour glucose level, *mmol/L (mg/dL)*	5.9 ± 0.06 (106.4 ± 1.11)	6.3 ± 0.05 (113.6 ± 0.92)	5.5 ± 0.08 (99.2 ± 1.35)	5.7 ± 0.07 (102.3 ± 1.21)
Systolic blood pressure, *mm Hg*	120.1 ± 0.49	113.1 ± 0.41	117.0 ± 0.60	110.0 ± 0.54
Diastolic blood pressure, *mm Hg*	74.8 ± 0.33	70.3 ± 0.27	73.0 ± 0.40	68.3 ± 0.35
Total cholesterol level, *mmol/L (mg/dL)*	5.4 ± 0.04 (208.0 ± 1.38)	5.1 ± 0.03 (198.6 ± 1.15)	5.2 ± 0.04 (202.2 ± 1.69)	5.2 ± 0.04 (201.2 ± 1.50)
LDL cholesterol level, *mmol/L (mg/dL)*	3.4 ± 0.03 (130.4 ± 1.26)	3.1 ± 0.03 (119.7 ± 1.05)	3.3 ± 0.04 (126.5 ± 1.54)	3.1 ± 0.04 (119.3 ± 1.37)
HDL cholesterol level, *mmol/L (mg/dL)*	1.2 ± 0.01 (46.2 ± 0.53)	1.4 ± 0.01 (54.3 ± 0.44)	1.3 ± 0.02 (48.6 ± 0.65)	1.6 ± 0.01 (60.6 ± 0.58)
Triglyceride level, *mmol/L (mg/dL)*	1.9 ± 0.04 (171.7 ± 3.28)	1.4 ± 0.03 (126.4 ± 2.73)	1.6 ± 0.05 (143.1 ± 4.00)	1.2 ± 0.04 (108.1 ± 3.57)
Body mass index, *kg/m²*	28.1 ± 0.19	27.9 ± 0.16	26.5 ± 0.23	24.8 ± 0.20
Family history of diabetes, %§	39.6	33.7	21.0	15.6

* Values with the plus/minus sign are the mean ± SE. HDL = high-density lipoprotein; LDL = low-density lipoprotein.
† *P* values are for the main effects of ethnicity, sex, and the interaction between ethnicity and sex.
‡ Unadjusted variable.
§ Participants were considered to have a family history if they had a parent or sibling with diabetes mellitus. This variable was adjusted for age by using logistic regression.

abetes status was indeterminate at follow-up. (Participants with indeterminate status had no evidence of diabetes but were missing values for at least one of the three study criteria for diabetes classification.) Of the 275 participants with incident diabetes, 221 were not receiving pharmacologic treatment for diabetes and were given a diagnosis exclusively on the basis of plasma glucose levels that met the WHO criteria (3). Of the 54 participants with confirmed pharmacologic treatment for diabetes, 45 also met one or both plasma glucose criteria for diabetes. Thus, only 9 incident cases of diabetes were diagnosed exclusively on the basis of medication history. The analyses presented here also exclude data on 101 persons with missing values for at least one predictor variable. Thus, our analyses are based on the data of 1791 Mexican Americans and 1112 non-Hispanic whites, of whom 204 Mexican Americans and 65 non-Hispanic whites developed diabetes.

Table 1 shows age-adjusted baseline characteristics of the study sample according to sex and ethnicity. We observed significant sex-by-ethnicity interactions for total and HDL cholesterol levels and for body mass index. The logistic regression coefficients, however, were not statistically significant for any of these interactions in the full or clinical model, and the global likelihood ratio test of these models with and without the interaction terms was likewise not significant. Therefore, we did not further consider models with interactions.

Table 2 shows the areas under the ROC curves, their 95% CIs, their Hosmer–Lemeshow goodness-of-fit statistics, and tests of the statistical significance of the differences between various models by using the DeLong algorithm (16) and, for comparison of nested models, likelihood ratio tests. The Hosmer–Lemeshow test did not reject the goodness of fit for any of the models.

The principal finding presented in **Table 2** is that all of the multivariable models outperformed the model that relies exclusively on the 2-hour glucose measurement in predicting future type 2 diabetes—that is, the areas under their ROC curves are in every case larger than the areas under the ROC curves for 2-hour glucose measurement alone. The multivariable model with the smallest area under its ROC curve—namely, the clinical model *without* 2-hour glucose—significantly outperformed the model consisting exclusively of the 2-hour glucose value; moreover, the other multivariable models performed at least as well as the model consisting of 2-hour glucose value alone. The full model with or without 2-hour glucose measurement was not significantly better than the corresponding clinical models. For both the full model and the clinical model, inclusion of the 2-hour glucose value significantly increased the areas under the ROC curves, but the improvements in both cases were less than 1.5%. (The 95% CIs obtained by the bootstrap procedure were similar to those shown in **Table 2** [obtained by using the DeLong algorithm].) The significance of the differences between areas under

Table 1—**Continued**

P Values for Main Effects and Interactions†		
Ethnicity	**Sex**	**Ethnicity × Sex**
<0.001	>0.2	>0.2
0.0393	<0.001	>0.2
<0.001	<0.001	0.0776
<0.001	<0.001	>0.2
<0.001	<0.001	>0.2
>0.2	<0.001	0.0038
0.1586	<0.001	0.1749
<0.001	<0.001	<0.001
<0.001	<0.001	0.1312
<0.001	0.001	<0.001
<0.0056	<0.001	>0.2

the ROC curves shown in Table 2 were also validated by the bootstrap procedure—that is, the 95% CIs of the differences in areas obtained by the bootstrap procedure excluded zero when the other tests were statistically significant and included zero when the other tests were not statistically significant. In particular, in 95% of replications the areas under the ROC curves for the models that included 2-hour glucose measurement exceeded the areas under the corresponding ROC curves that excluded 2-hour glucose value by not more than 2.8% and not less than 0.5%. The parameter estimates for the clinical model with the 2-hour glucose value excluded are given in the Appendix. The parameter estimates for the other models are available from the authors upon request.

The **Figure** provides a visual representation of selected ROC curves and shows that both multivariable models are superior to the model based exclusively on 2-hour glucose value. The position of impaired glucose tolerance on the 2-hour glucose curve is indicated. The sensitivity and false-positive rate of impaired glucose tolerance are 50.9% and 10.2%, respectively. The **Figure** shows that at the same false-positive rate, the clinical model has slightly better sensitivity. However, this sensitivity and false-positive rate can be achieved by using the clinical model without performing an oral glucose tolerance test. If a higher sensitivity is desired, the clinical model is clearly superior to relying on the 2-hour glucose value alone.

DISCUSSION

Overwhelmingly, the method used for identifying persons at high risk for diabetes in research applications has been to select persons with impaired glucose toler-

Table 2. **Areas under Receiver-Operating Characteristic Curves for Models Predicting the 7.5-Year Incidence of Type 2 Diabetes Mellitus in the San Antonio Heart Study***

Models and Model Comparisons	Area Under the Receiver-Operating Characteristic Curve (95% CI), %	*P* Value (Hosmer–Lemeshow)†	*P* Values for Model Comparisons	
			DeLong‡	Likelihood Ratio Test§
Models				
Full model with 2-h glucose	85.9 (83.6–88.3)	>0.2		
Full model—no 2-h glucose	84.5 (82.0–87.0)	0.12		
Clinical model with 2-h glucose	85.7 (83.4–88.2)	>0.2		
Clinical model—no 2-h glucose	84.3 (81.8–86.7)	>0.2		
2-Hour glucose	77.5 (74.3–80.7)	0.20		
Comparisons between models				
Full model with 2-h glucose vs. full model—no 2-h glucose			0.020	<0.001
Full model with 2-h glucose vs. clinical model with 2-h glucose			0.105	>0.2
Full model—no 2-h glucose vs. clinical model—no 2-h glucose			0.079	0.18
Clinical model with 2-h glucose vs. clinical model—no 2-h glucose			0.015	<0.001
Clinical model—no 2-h glucose vs. 2-h glucose			<0.001	—‖

* The models assessed were full or clinical multivariable models with or without 2-hour plasma glucose value and 2-hour plasma glucose level only. The clinical multivariable models used the following variables: age, sex, ethnicity, fasting glucose level, systolic blood pressure, high-density lipoprotein cholesterol level, body mass index, and parent or sibling with diabetes. The full multivariable models included all variables from the clinical model plus diastolic blood pressure, total and low-density lipoprotein cholesterol levels, and triglyceride level.

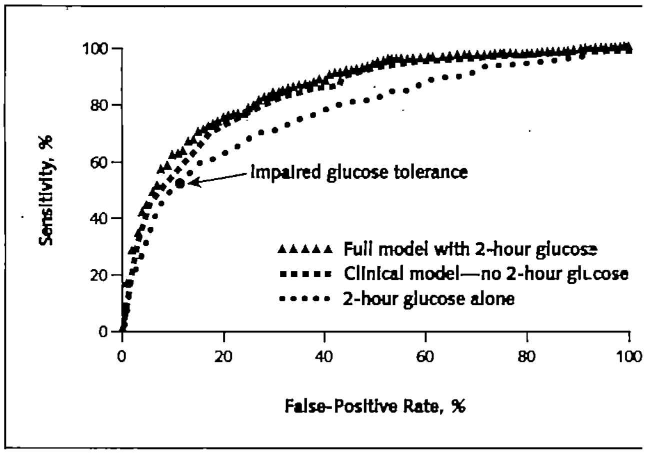
† *P* values calculated by using the Hosmer–Lemeshow goodness-of-fit test.

‡ *P* values for test of difference in areas under two receiver-operating characteristic curves; calculated by using the method developed by DeLong and colleagues (16).

§ *P* value for the likelihood ratio test.

‖ Not applicable for nonnested models.

Figure. **Receiver-operating characteristic curves for the full multivariable model with 2-hour glucose value included, the clinical model with the 2-hour glucose measurement excluded, and the 2-hour glucose variable by itself.**



The location (*large circle*) of impaired glucose tolerance (plasma glucose level ≥7.8 mm/L [≥140 mg/dL]) on the 2-hour glucose curve is indicated.

ance with minimal or no regard to other diabetes risk factors (7–9). Impaired glucose tolerance is defined by the plasma glucose level measured 2 hours after an oral glucose load; thus, a 2-hour glucose tolerance test is necessary to identify persons in this category. Because of its cost and inconvenience, the oral glucose tolerance test has been met with considerable resistance and is rarely used in ordinary clinical practice (4, 18). Because clinical trials have documented that diabetes can be prevented by behavioral or pharmacologic interventions (7–9), there is a need to develop methods to identify persons at high risk for diabetes by using techniques that will be widely accepted in clinical and public health settings, not just in research settings. Our results suggest that using a simple multivariable model—consisting of readily available clinical measurements, most of which are routinely gathered anyway, and not requiring a 2-hour oral glucose tolerance test—is superior to relying exclusively on the 2-hour glucose value for identifying persons at high risk for future type 2 diabetes. We believe that this simple clinical model will be more readily accepted by clinicians because it contains fewer variables and is not significantly inferior to the full model in predictive discrimination. Although the addition of the 2-hour glucose value to either multivariable model improved its predictive discrimination even further, the improvements were minor relative to the differences in predictive discrimination between the multivariable models and exclusive reliance on 2-hour glucose value. Moreover, addition of the 2-hour glucose value to the multivariable models would probably undermine patients' and clinicians' acceptance of this method (4, 18).

Although the 2-hour glucose value may add little to identifying persons at risk for future diabetes, oral glucose tolerance tests are arguably still needed to diagnose prevalent cases of diabetes in which the only manifestation of the disease is an abnormal 2-hour glucose value. Although the American Diabetes Association has taken the position that identifying such cases is not mandatory (4), the WHO has dissented from this viewpoint (3). A full discussion of this matter is beyond the scope of the present paper; however, it should be noted that no clinical trial has ever focused specifically on the benefits of treating such patients instead of waiting until they manifest fasting hyperglycemia. Moreover, patients whose diabetes is diagnosed solely on the basis of an abnormal 2-hour value have a high rate of reversion to normal on follow-up and may in fact represent false-positive diagnoses. We have previously reported, for example, that such cases were almost 5 times more likely to revert to nondiabetic status after 7 to 8 years of follow-up compared with persons meeting conventional fasting or clinical diagnostic criteria (19).

In addition to inconvenience, cost is another obstacle to the widespread adoption of the 2-hour oral glucose tolerance test as a screening tool for identifying persons with impaired glucose tolerance. The American Diabetes Association has recommended screening criteria for diabetes (4). The clinical model, the details of which are given in the Appendix, could be incorporated as it stands into clinical practice and public health practice with the aid of a hand-held, programmable calculator or a personal computer. The model could be used in clinical practice to support patient counseling and in public health practice to identify target populations for preventive interventions. Before such a clinical and public health tool is adopted, however, certain limitations of the present study need to be acknowledged. First, the estimates of the model parameters could be biased by the persons whose diabetic status was unknown because of missing data at baseline or follow-up or because they died before follow-up. This limitation indicates a need to validate the model in other populations. In addition to further validation in populations similar to those in our analysis, the model should be validated in other high-risk ethnic groups, such as Native Americans and African Americans, as well as non-U.S. populations. Clearly, we cannot state with confidence that our model would perform satisfactorily in these ethnic groups because they were not included in the present study. Because the development of diabetes has been studied in many prospective cohort studies, most of which have contained all, or at least most, of the risk factors in our analysis, we hope that this report will stimulate other researchers with suitable databases to evaluate prediction models for type 2 diabetes similar to those presented here.

APPENDIX

The following are parameter estimates for the clinical model without the value for the glucose level obtained 2 hours after the administration of an oral glucose load:

$p = 1/(1 - e^{-x})$, where $x = -13.415 + 0.028(\text{age}) + 0.661(\text{sex}) + 0.412(\text{MA}) + 0.079(\text{FG}) + 0.018(\text{SBP}) - 0.039(\text{HDL}) + 0.070(\text{BMI}) + 0.481(\text{family history})$. In this equation, p = the probability of developing diabetes over the 7.5 year follow-up period; age is in years; sex = 1 if female, 0 if male; MA = 1 if Mexican American, 0 if non-Hispanic white; FG = fasting glucose in mg/dL; SBP = systolic blood pressure in mm Hg; HDL = high-density lipoprotein cholesterol level in mg/dL; BMI = body mass index in kg/m^2; and family history = 1 if at least one parent or sibling has diabetes or 0 if not.

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High Risk for Hyperlipidemia and the Metabolic Syndrome after an Episode of Hypertriglyceridemia during 13-*cis* Retinoic Acid Therapy for Acne: A Pharmacogenetic Study

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Background: **Administration of 13-*cis* retinoic acid (isotretinoin) for acne is occasionally accompanied by hyperlipidemia. It is not known why some persons develop this side effect.**

Objective: **To determine whether isotretinoin triggers a familial susceptibility to hyperlipidemia and the metabolic syndrome.**

Design: **Cross-sectional comparison.**

Setting: **University hospital in Lausanne, Switzerland.**

Participants: **102 persons in whom triglyceride levels increased at least 1.0 mmol/L (≥89 mg/dL) (hyperresponders) and 100 persons in whom triglyceride levels changed 0.1 mmol/L (≤9 mg/dL) or less (nonresponders) during isotretinoin therapy for acne. Parents of 71 hyperresponders and 60 nonresponders were also evaluated.**

Measurements: **Waist-to-hip ratio; fasting glucose, insulin, and lipid levels; and *apoE* genotype.**

Results: **Hyperresponders and nonresponders had similar pretreatment body weight and plasma lipid levels. When reevaluated approximately 4 years after completion of isotretinoin therapy, hyperresponders were more likely to have hypertriglyceridemia (triglyceride level > 2.0 mmol/L [>177 mg/dL]; odds ratio [OR], 4.8 [95% CI, 1.6 to 13.8]), hypercholesterolemia (cholesterol level > 6.5 mmol/L [>252 mg/dL]; OR, 9.1 [CI, 1.9 to 43]), truncal obesity (waist-to-hip ratio > 0.90 [OR, 11.0 (CI, 2.0 to 59]), and hyperinsulinemia (insulin–glucose ratio > 7.2; OR, 3.0 [CI, 1.6 to 5.7]). In addition, more hyperresponders had at least one parent with hypertriglyceridemia (OR, 2.6 [CI, 1.2 to 5.7]) or a ratio of total to high-density lipoprotein cholesterol that exceeded 4.0 (OR, 3.5 [CI, 1.5 to 8.0]). Lipid response to isotretinoin was closely associated with the *apoE* gene.**

Conclusion: **Persons who develop hypertriglyceridemia during isotretinoin therapy for acne, as well as their parents, are at increased risk for future hyperlipidemia and the metabolic syndrome.**

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Lipid abnormalities have been associated with the use of various pharmacologic agents, including β-blockers, diuretics, estrogens, HIV-1 protease inhibitors (1), and 13-*cis* retinoic acid (isotretinoin [Accutane], Roche, Basel, Switzerland) (2, 3). Isotretinoin is the treatment of choice for severe acne resistant to other treatments. In some patients (20%), isotretinoin causes a marked but reversible elevation in plasma concentrations of triglyceride-rich lipoproteins, which can result in acute pancreatitis (4). The severity of this complication has prompted dermatologists to systematically monitor fasting plasma lipid levels whenever they prescribe isotretinoin. The mechanism for isotretinoin-induced hyperlipidemia remains elusive, and it is not known why only a fraction of persons develop this side effect.

It is possible that isotretinoin elevates plasma triglyceride levels in patients with acne who have a latent, possibly familial and genetic predisposition to hyperlipidemia. The most common form of familial lipid disorders is familial combined hyperlipidemia (5). This condition shares a series of features with the metabolic syndrome, a multifaceted condition characterized by hyperlipidemia, hypertension, hyperuricemia, insulin resistance, diabetes, and obesity (6–10). Familial combined hyperlipidemia and the metabolic syndrome are usually dormant during childhood and become progressively apparent in adults. Both conditions are major contributors to heart disease. Although these disorders have a familial component (5, 11), the responsible genes have not been identified. Elucidation of the genetic basis of familial combined hyperlipidemia and the metabolic syndrome has been hampered by the heterogeneity of these disorders and their incomplete penetrance, which are consistent with strong gene–environment interactions. We reasoned that isotretinoin is an environmental trigger that unmasks a latent familial predisposition to hyperlipidemia and the metabolic syndrome.

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To test our hypothesis, we used a family-based cross-sectional comparison. We initially identified a large group of young adults who had developed a pronounced elevation in plasma triglyceride levels during isotretinoin therapy for acne (hyperresponders) and an equally large group whose plasma triglyceride levels had not changed during therapy (nonresponders). All participants were reevaluated for markers of the metabolic syndrome while not receiving therapy. Parents of hyperresponders and nonresponders were also evaluated.

METHODS

Study Design and Participants

Initially, we examined the medical records of 613 persons with acne who had been treated with isotretinoin for at least 4 weeks between 1988 and 1998 at the dermatology division of CHUV University Hospital and at the practices of four dermatologists in the area of Lausanne, Switzerland. For 601 participants (98%), fasting plasma lipid levels had been measured once before initiation of isotretinoin therapy and had then been monitored monthly by the same laboratory. A total of 18 persons were excluded because they had fasting pretreatment plasma cholesterol levels of 7.0 mmol/L or more (≥271 mg/dL), triglyceride levels of 3.0 mmol/L or more (≥266 mg/dL), or both. Thus, 583 persons were included in the analysis (**Figure 1**). Mean duration of isotretinoin course was 6 months, and an average of six lipid values were available for each participant during treatment. We determined isotretinoin-associated changes in fasting plasma triglyceride level by calculating the difference between the highest value recorded during isotretinoin therapy and the pretreatment level. Hyperresponders ($n = 117$) were identified as persons who had developed an increase in plasma triglyceride level of 1.0 mmol/L or more (≥89 mg/dL) (corresponding to the upper quintile in the distribution); 145 participants whose plasma triglyceride levels had remained unchanged or decreased during isotretinoin therapy (a difference ≤ 0.1 mmol/L [≤9 mg/dL], corresponding to the lower quartile in the distribution) were considered nonresponders. We contacted the hyperresponders and the nonresponders and asked them to participate in our study and to be reevaluated while not receiving therapy. Only 15 hyperresponders and 45 nonresponders were not found or declined to participate. Participation rate was higher for hyperresponders (87%) than nonresponders (69%) ($P = 0.001$) because of difficulties in motivating healthy persons who had shown no change in plasma lipid levels during isotretinoin therapy. A total of 102 hyperresponders and 100 nonresponders were reevaluated while not receiving therapy. We also contacted the parents of these participants (when both parents were available) and eventually recruited both parents of 71 hyperresponders and 60 nonresponders. The procedures were in accordance with institutional guidelines. The local Ethics Committee approved the protocol, and each participant provided informed consent.

Context

Isotretinoin (Accutane, Roche, Basel, Switzerland) is the treatment of choice for severe acne that is resistant to topical treatment.

Approximately 20% of patients develop marked elevations in triglyceride levels.

The mechanism responsible for isotretinoin-induced hyperlipidemia is unknown.

Contribution

This study showed that isotretinoin-induced hypertriglyceridemia identifies patients at high risk for chronic hyperlipidemia, truncal obesity, and hyperinsulinemia.

The *apoE* gene and $\epsilon 2$ and $\epsilon 4$ alleles were more common in patients with isotretinoin-induced hypertriglyceridemia than in patients who had no lipid abnormalities while taking the drug.

Implications

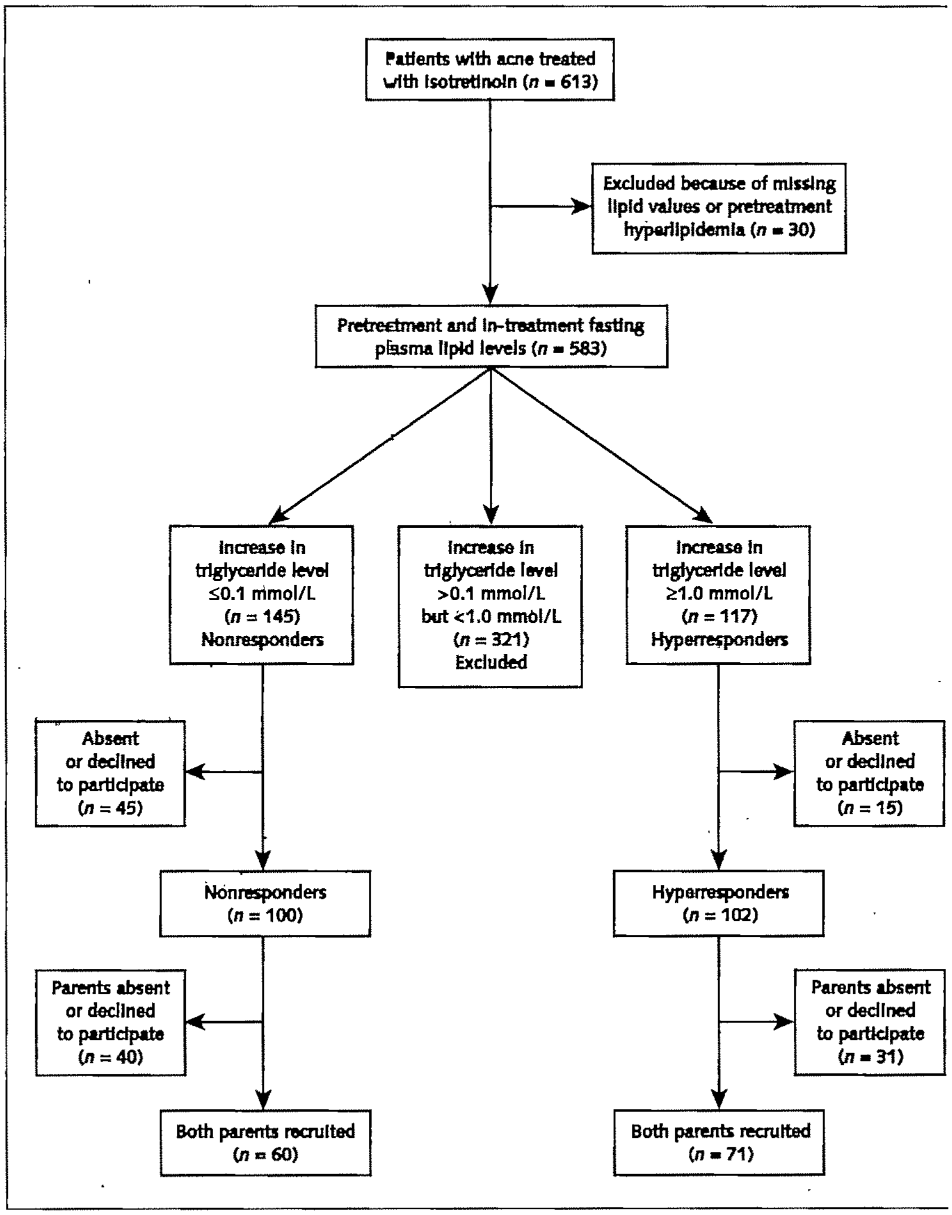
People with isotretinoin-induced hypertriglyceridemia have increased risks for chronic hyperlipidemia and the metabolic syndrome that are possibly related to the *apoE* gene.

–The Editors

Measurements

Participants filled out a questionnaire and had a physical examination, including measurement of height, body weight, waist-to-hip ratio, and blood pressure (evaluated using a sphygmomanometer while participants were seated for ≥10 minutes). Fat mass was estimated by bioelectric impedance using the Bio-Z generator (Eugédia, Paris, France), as described elsewhere (12). Venous blood was collected on EDTA after a 12-hour fast and was processed within 2 hours. Nineteen parents receiving lipid-lowering therapy were asked to stop therapy at least 1 week before they were examined. The clinical chemistry laboratory of Lausanne University Medical Policlinic performed bio-

Figure 1. **Flow chart of the study.**


Patients with acne treated with isotretinoin (*n* = 613)
Excluded because of missing lipid values or pretreatment hyperlipidemia (*n* = 30)
Pretreatment and in-treatment fasting plasma lipid levels (*n* = 583)
Increase in triglyceride level ≤0.1 mmol/L (*n* = 145) Nonresponders
Increase in triglyceride level >0.1 mmol/L but <1.0 mmol/L (*n* = 321) Excluded
Increase in triglyceride level ≥1.0 mmol/L (*n* = 117) Hyperresponders
Absent or declined to participate (*n* = 45)
Absent or declined to participate (*n* = 15)
Nonresponders (*n* = 100)
Hyperresponders (*n* = 102)
Parents absent or declined to participate (*n* = 40)
Parents absent or declined to participate (*n* = 31)
Both parents recruited (*n* = 60)
Both parents recruited (*n* = 71)

To convert mmol/L to mg/dL, divide by 0.0113.

chemical measurements, as described elsewhere (1). Genomic DNA was isolated from peripheral blood cells, and a series of sequence variations was examined by using polymerase chain reaction amplification and restriction digest, according to published protocols: the ε2, ε3, and ε4 alleles within the *apoE* gene (13); the *Pro12Ala* polymorphism within the peroxisome proliferator-activated receptor (*PPAR*)-γ gene (14); the C to A substitution at position −278 within the 5′ flanking region of the cholesterol 7α-hydroxylase (*CYP7-α*) gene (15); and the *Sst*I, *Xmn*I and *Msp*I polymorphisms within the *apoAI-CIII-AIV* genes (16).

Statistical Analyses

Data are presented as the mean (±SD). Statistical analyses were performed by using SPSS, version 10.0 (SPSS, Inc., Chicago, Illinois). We used *t*-tests, or Wilcoxon rank-sum tests when appropriate, to compare clinical characteristics. For comparison of frequency distribution, we used the chi-square test or the Fisher exact test. Logistic regression analysis was used to calculate the risk for metabolic disorders associated with a previous elevation in plasma triglyceride levels during isotretinoin therapy. The same type of analysis was performed to evaluate the risk in hyperresponders and nonresponders having one or two parents with metabolic disorders.

Role of the Funding Sources

None of the funding sources had any role in the design of the study; the collection, analysis, and interpretation of the data; or the decision to submit the manuscript for publication.

RESULTS

Changes in Plasma Triglyceride Levels during Isotretinoin Therapy

Isotretinoin-associated changes in fasting plasma triglyceride level ranged from −0.95 mmol/L (−84 mg/dL) to 3.75 mmol/L (332 mg/dL). Average change was 0.57 ± 0.67 mmol/L (50 ± 59 mg/dL). Compared with nonresponders ($n = 100$), hyperresponders ($n = 102$) had similar pretreatment body weight (63.3 ± 9.6 kg vs. 64.4 ± 11.4 kg; $P > 0.2$) and plasma levels of total cholesterol (4.6 ± 0.8 mmol/L [176 ± 32 mg/dL] vs. 4.8 ± 1.0 mmol/L [186 ± 37 mg/dL]; $P = 0.07$) and triglycerides (1.1 ± 0.4 mmol/L [101 ± 38 mg/dL] vs. 1.2 ± 0.5 mmol/L [104 ± 42 mg/dL]; $P > 0.2$). Hyperresponders had received a 10% higher dosage of isotretinoin (0.53 ± 0.11 mg/kg of body weight vs. 0.59 ± 0.14 mg/kg of body weight; $P = 0.003$).

Characteristics of Hyperresponders and Nonresponders When Not Receiving Isotretinoin Therapy

Hyperresponders and nonresponders were reevaluated 3.8 ± 2.5 years (median, 4 years) after completion of isotretinoin therapy. Mean age was 27.4 ± 7.2 years (range, 16 to 49 years; median, 26 years). In contrast to the pretreatment period, hyperresponders had a higher body mass index and higher fasting plasma concentrations of total cholesterol and triglycerides than nonresponders (**Table 1**). Moreover, waist-to-hip ratio; fat mass content; systolic blood pressure; plasma levels of low-density lipoprotein cholesterol, apolipoprotein B, and insulin; ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol; and ratio of insulin to glucose were all higher in hyperresponders.

To further characterize the relationship between the lipid response to isotretinoin therapy and the subsequent development of metabolic disorders, we performed logistic regression analysis, using age, sex, *apoE* genotype, and dose of isotretinoin as covariates (**Figure 2**). This analysis indicated that a previous elevation of 1.0 mmol/L or greater (≥89 mg/dL) in plasma triglyceride levels during isotretinoin therapy was associated with an increased risk for hypertriglyceridemia (triglyceride level > 2.0 mmol/L [>177 mg/dL]; odds ratio [OR], 4.8 [95% CI, 1.6 to 13.8]), hypercholesterolemia (cholesterol level > 6.5 mmol/L [>252 mg/dL]; OR, 9.1 [CI, 1.9 to 43]), truncal obesity (waist-to-hip ratio > 0.90; OR, 11.0 [CI, 2.0 to 59]), and hyperinsulinemia (insulin–glucose ratio > 7.2; OR, 3.0 [CI, 1.6 to 5.7]).

The metabolic syndrome is characterized by the aggregation of various disorders. We determined how many of five disorders were present in each participant while not receiving therapy. We considered hypertriglyceridemia (>2.0 mmol/L [>177 mg/dL]), hypercholesterolemia (>6.5 mmol/L [252 mg/dL]), hyperinsulinemia (insulin–glucose ratio > 7.2), elevated body weight (body mass index > 25 kg/m^2), and hypertension (systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or both). Hyperresponders had, on average, two times more disorders than nonresponders (1.5 ± 1.3 vs. 0.8 ± 0.8; $P < 0.001$). Moreover, 40 of 102 hyperresponders had two or more of these conditions, compared with 13 of 100 nonresponders (adjusted odds ratio, 5.6 [CI, 2.5 to 12.4]; $P < 0.001$).

Clinical Characteristics of the Parents

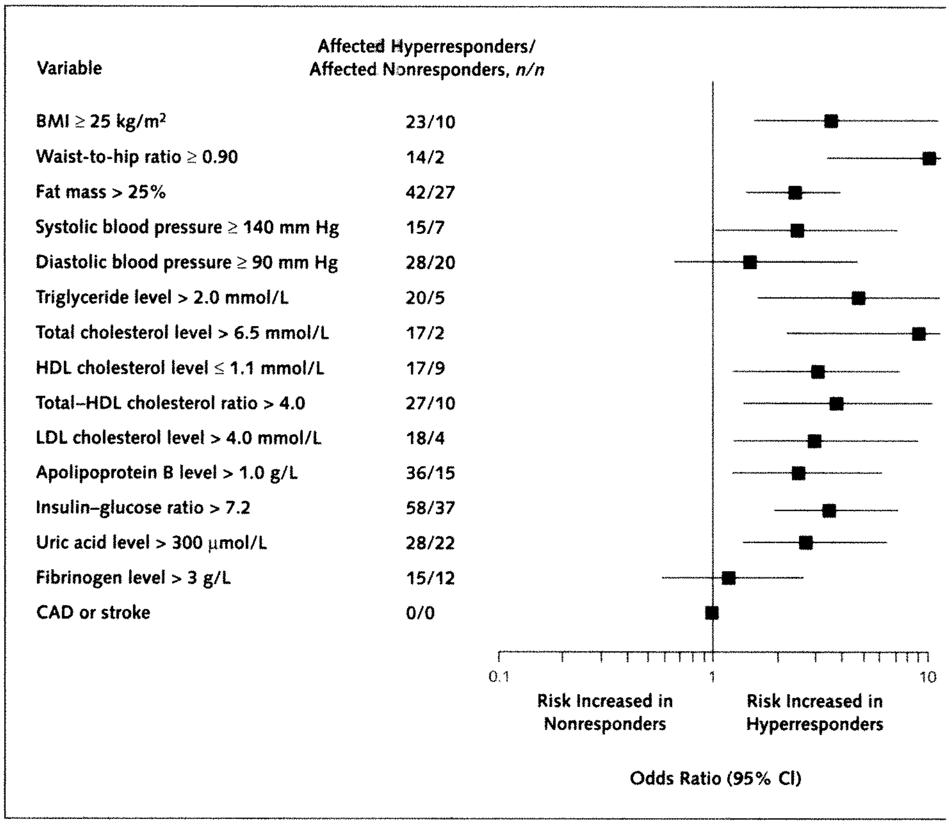
To explore the familial component of the lipid response to isotretinoin therapy, we also examined both parents of 71 hyperresponders and 60 nonresponders for markers of the metabolic syndrome. Both fathers and mothers of hyperresponders had higher plasma triglyceride levels and a higher ratio of total to HDL cholesterol than fathers and mothers of nonresponders (**Table 1**). In addition, the proportion of hyperresponders who had none, one, or two parents with hypertriglyceridemia

Table 1. **Characteristics of Hyperresponders and Nonresponders and Their Parents While Not Receiving Isotretinoin Therapy**

Characteristic	Hyperresponders (n = 102)	Nonresponders (n = 100)	*P* Value	Fathers of Hyperresponders (n = 71)	Fathers of Nonresponders (n = 60)	*P* Value
Age, *y*	28.1 ± 7.0	26.7 ± 7.3	0.17	55.8 ± 7.5	56.5 ± 7.4	>0.2
Sex (male/female), *n/n*	50/52	52/48	>0.2			
Body mass index, *kg/m²*	22.9 ± 3.5	21.7 ± 2.7	0.005	26.6 ± 4.4	26.3 ± 3.0	>0.2
Waist-to-hip ratio	0.80 ± 0.08	0.77 ± 0.06	0.02	0.94 ± 0.06	0.93 ± 0.06	>0.2
Fat mass, %	21.9 ± 7.1	19.5 ± 6.7	0.02	23.3 ± 7.5	23.0 ± 7.4	>0.2
Systolic blood pressure, *mm Hg*	125 ± 13	121 ± 10	0.03	137 ± 14	136 ± 17	>0.2
Diastolic blood pressure, *mm Hg*	85 ± 8	83 ± 7	0.11	93 ± 8	91 ± 8	0.14
Triglycerides, *mmol/L (mg/dL)*	1.5 ± 0.7 (132 ± 60)	1.0 ± 0.4 (91 ± 39)	<0.001	2.0 ± 1.5 (174 ± 134)	1.5 ± 0.7 (136 ± 65)	0.05
Total cholesterol, *mmol/L (mg/dL)*	5.1 ± 1.2 (197 ± 47)	4.7 ± 0.9 (180 ± 37)	0.004	6.3 ± 1.2 (246 ± 46)	6.0 ± 0.9 (234 ± 34)	0.10
HDL cholesterol, *mmol/L (mg/dL)*	1.5 ± 0.4 (58 ± 16)	1.6 ± 0.4 (63 ± 15)	0.05	1.4 ± 0.3 (55 ± 13)	1.5 ± 0.3 (58 ± 13)	0.16
LDL cholesterol, *mmol/L (mg/dL)*	2.9 ± 1.1 (112 ± 41)	2.6 ± 0.8 (99 ± 31)	0.01	4.0 ± 1.1 (157 ± 43)	3.8 ± 0.8 (148 ± 31)	>0.2
Ratio of total to HDL cholesterol	3.6 ± 1.1	3.0 ± 0.7	<0.001	4.8 ± 1.6	4.2 ± 1.1	0.01
Apolipoprotein B level, *g/L*	1.0 ± 0.3	0.8 ± 0.2	<0.001	1.3 ± 0.3	1.2 ± 0.2	0.08
Insulin, *pmol/L*	49 ± 48	38 ± 22	0.03	51 ± 38	41 ± 29	0.09
Insulin–glucose ratio	9.7 ± 10.0	7.2 ± 3.9	0.02	8.6 ± 6.5	7.2 ± 5.7	0.11
Uric acid, *µmol/L*	264 ± 66	250 ± 58	0.09	321 ± 60	303 ± 54	0.07
Fibrinogen, *g/L*	2.6 ± 0.5	2.4 ± 0.4	0.10	2.8 ± 0.7	2.8 ± 0.5	>0.2

* Values presented with a plus/minus sign are the mean ± SD. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Figure 2. **Risk for metabolic disorders according to the previous lipid response to isotretinoin therapy for acne in 102 hyperresponders and 100 nonresponders.**



Odds ratios were calculated by using logistic regression analysis after adjustment for age, sex, *apoE* genotype, and dosage of isotretinoin. BMI = body mass index; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein. To convert triglyceride values to mg/dL, divide by 0.0113; to convert total, HDL, and LDL cholesterol values to mg/dL, divide by 0.0259.

Table 1—**Continued**

Mothers of Hyperresponders ($n = 71$)	Mothers of Nonresponders ($n = 60$)	*P* Value
53.9 ± 5.5	52.8 ± 6.9	>0.2
25.0 ± 4.9	24.0 ± 3.9	>0.2
0.81 ± 0.08	0.79 ± 0.08	0.14
29.9 ± 8.3	29.3 ± 6.7	>0.2
137 ± 19	131 ± 15	0.07
88 ± 9	88 ± 9	>0.2
1.5 ± 0.6 (137 ± 56)	1.2 ± 0.4 (107 ± 39)	0.001
6.2 ± 1.1 (239 ± 44)	5.9 ± 0.9 (228 ± 37)	0.11
1.8 ± 0.4 (71 ± 16)	1.9 ± 0.4 (75 ± 16)	0.10
3.6 ± 1.1 (140 ± 43)	3.4 ± 0.9 (131 ± 38)	0.19
3.6 ± 1.1	3.2 ± 0.9	0.02
1.1 ± 0.3	1.0 ± 0.2	0.05
41 ± 28	35 ± 22	0.16
7.2 ± 4.3	6.5 ± 3.6	0.16
242 ± 62	226 ± 53	0.12
2.8 ± 0.7	2.8 ± 0.5	>0.2

was 57%, 34%, and 9%, respectively, compared with 78%, 22%, and 0% in nonresponders ($P = 0.01$). Sixteen percent, 64%, and 20% of hyperresponders and 40%, 55%, and 5% of nonresponders had no parents, one parent, or both parents with a ratio of total to HDL cholesterol exceeding 4.0 ($P = 0.002$). The odds ratios for having one or two parents with markers of the metabolic syndrome are described in **Figure 3**. In hyperresponders, the risk for having at least one parent with hypertriglyceridemia and a ratio of total to HDL cholesterol greater than 4.0 was 2.6 (CI, 1.2 to 5.7) and 3.5 (CI, 1.5 to 8.0), respectively. Overall, parents of hyperresponders had, on average, more disorders than parents of nonresponders (2.3 ± 1.5 vs. 1.8 ± 1.4; $P = 0.01$). In addition, 64 of 138 parents of hyperresponders had three or more disorders, compared with 39 of 114 parents of nonresponders ($P = 0.03$) (adjusted odds ratio, 1.7 [CI, 1.0 to 2.9]; $P = 0.04$). Alcohol consumption and drug use (antihypertensive agents or hormone replacement therapy) did not differ between the two groups. Similar findings were observed when 19 parents who were taking lipid-lowering therapy were excluded from the analysis.

Molecular Analyses of Selected Gene Polymorphisms

To examine the genetic basis of the lipid response to isotretinoin therapy, we analyzed a series of common sequence variants known to be associated with familial forms of lipid disorders (**Table 2**). A significant association was observed between the *apoE* gene and isotretinoin-induced elevation in plasma triglyceride levels. Both *apoE* $\epsilon2$– and apoE $\epsilon4$–containing genotypes were overrepresented among hyperresponders. In addition, the frequency of the *apoE* $\epsilon2$, $\epsilon3$, and $\epsilon4$ alleles differed significantly among hyperresponders (14.0%, 70.5%, and 15.5%, respectively), nonresponders (6.5%, 85.0%, and 8.5%, respectively; $P = 0.002$), and a population of 174 nondiabetic persons recruited locally (17) (10.7%, 82.1%, and 7.2%, respectively; $P = 0.005$). The frequency of *apoE* alleles was similar in nonresponders and in the local population ($P > 0.2$). The frequency of distribution of the sequence variants examined within the genes encoding *PPAR-γ*, *apoAI-CIII-AIV*, or *CYP7-α* was similar to that reported in the literature (13, 15, 16). Apart from the *Xmn*I polymorphism within the *ApoA1* gene, the difference in the frequency of distribution of the various alleles or genotypes between hyperresponders and nonresponders did not reach statistical significance, and no significant association was detected on transmission disequilibrium tests (18).

DISCUSSION

Our study shows that young adults who previously had developed elevated plasma triglyceride levels during isotretinoin therapy for acne are at increased risk for future truncal obesity, hypercholesterolemia, hypertriglyceridemia, hyperinsulinemia, and hyperuricemia, all of which are markers of the metabolic syndrome (6–8). Hyperresponders were more likely than nonresponders to have one or two dyslipidemic parents. Finally, the lipid response to isotretinoin therapy was closely associated with the *apoE* gene. Taken together, these data are consistent with the hypothesis that isotretinoin exacerbates the phenotypic expression of a latent, partly familial and genetic predisposition to hyperlipidemia and the metabolic syndrome in hyperresponders. Conversely, nonresponders may be protected against these conditions.

This family-based study takes advantage of the adverse side effects of a particular drug to investigate the genetics of hyperlipidemia. We believe that this type of study may pave the way to a pharmacogenetic approach to familial combined hyperlipidemia and the metabolic syndrome and, possibly, to other complex traits. In addition, our data indicate that pharmacogenetics may prove useful in identifying patients with acne who are at increased risk for isotretinoin-induced hyperlipidemia.

We selected participants by using retrospective analysis of medical records. This approach was possible because dermatologists routinely monitor fasting lipid levels before and during isotretinoin therapy. Although this strategy was limited, it had several advantages. The metabolic syndrome is barely apparent in young adults at the age when they develop acne, and a follow-up period of several years would have been necessary to detect differences between hyperresponders and nonresponders in a prospective study. This strategy also enabled us to identify a large number of persons with acne who were previously treated with isotretinoin at a single medical center. Finally, this design allowed us to compare hyperresponders with nonresponders rather than with persons who had an average lipid response to isotretinoin. By increasing the contrast between the two groups, we were able to limit the sample size of participants who were reevaluated when not receiving therapy. However, we cannot formally exclude the possibility that our design may have slightly overestimated the association between the lipid response to isotretinoin therapy and the subsequent risk for hyperlipidemia and the metabolic syndrome.

In summary, our study shows that persons who become hypertriglyceridemic during isotretinoin therapy for acne, as well as their parents, are at increased risk for hyperlipidemia and the metabolic syndrome. We propose that close, long-term monitoring of blood pressure, plasma lipid levels, and body weight should be performed for such persons.

From CHUV University Hospital, University Medical Policlinic, and University of Lausanne, Lausanne; and Kantonsspital, St-Gallen, Switzerland.

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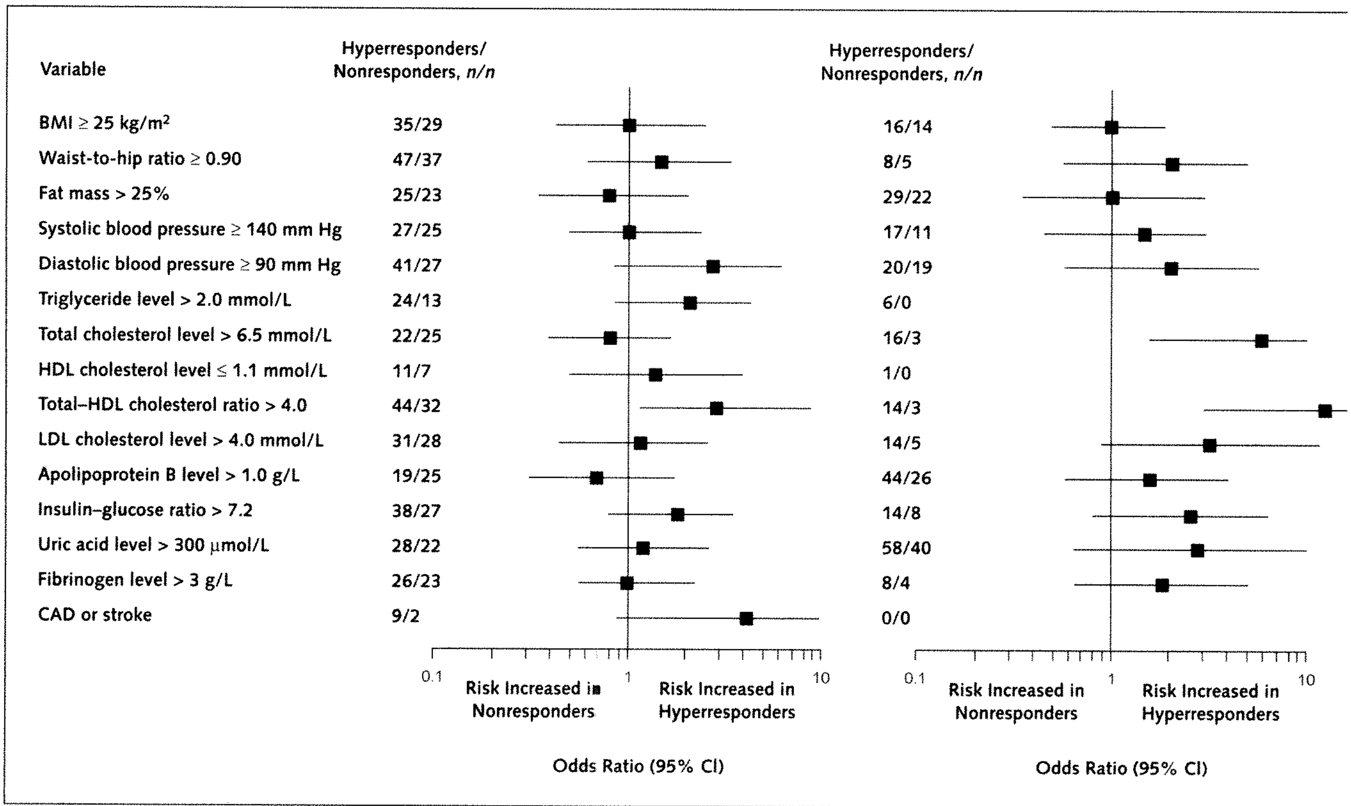
Figure 3. **Risk for metabolic disorders in parents of 71 hyperresponders and 60 nonresponders.**



Logistic regression analysis was used to calculate the risk for having one (*left*) or two (*right*) parents with metabolic disorders. BMI = body mass index; CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein. To convert triglyceride values to mg/dL, divide by 0.0113; to convert total, HDL, and LDL cholesterol values to mg/dL, divide by 0.0259.

Table 2. **Genotype Frequency of Selected Genes in 102 Hyperresponders and 100 Nonresponders***

Gene	Genotype	Hyperresponders, %	Nonresponders, %	*P* Value†	Odds Ratio (95% CI)‡	*P* Value†
ApoE	E3-E3	50	72	0.006	1.0 (reference)	
	E2-E2, E2-E3, or E2-E4	25	13		2.6 (1.2–5.6)	0.01
	E3-E4 or E4-E4	25	15		2.6 (1.2–5.4)	0.02
PPAR-γ	Pro12-Pro12	81	88	0.14	1.0 (reference)	
	Pro12-Ala12 or Ala12-Ala12	19	12		1.7 (0.8–3.6)	0.20
CYP7-α	−278A-−278A	34	37	>0.2	1.0 (reference)	
	−278A-−278C	44	50		0.6 (0.2–1.3)	0.17
	−278C-−278C	22	13		0.5 (0.2–1.2)	0.13
ApoA1-Msp1§	M1-M1	62	59	>0.2	1.0 (reference)	
	M1-M2 or M2-M2	38	41		0.9 (0.5–1.7)	>0.2
ApoA1-Xmn1§	X1-X1	83	68	0.01	1.0 (reference)	
	X1-X2 or X2-X2	17	32		0.5 (0.2–1.0)	0.04
ApoC3-Sst1§	S1-S1	74	82	0.09	1.0 (reference)	
	S1-S2 or S2-S2	26	18		1.6 (0.8–3.3)	0.19

* For technical reasons, genotypes were missing for 1 to 4 of 202 participants.
† Determined by using the chi-square test.
‡ Risk for being a hyperresponder in carriers of the rarer genotype, after adjustment for age, sex, and dosage of isotretinoin.
§ According to the nomenclature in reference 16.

tave Botnar and Placide Nicod Foundation; the Michel Tossizza Foundation; and Multidisciplinary Priority Project, Lausanne University.

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Severe Hepatotoxicity Associated with the Dietary Supplement LipoKinetix

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Lori A. Love, MD, PhD; and Tse-Ling Fong, MD

Background: LipoKinetix (Syntrax, Cape Girardeau, Missouri) is a dietary supplement marketed for weight loss.

Objective: To describe a possible causal association between LipoKinetix and hepatotoxicity.

Design: Case series.

Setting: Outpatient clinic, tertiary care hospital, and U.S. Food and Drug Administration databases.

Intervention: Routine medical and supportive care.

Measurements: Clinical and laboratory evaluation.

Results: All patients developed acute hepatotoxicity within 3 months of starting LipoKinetix. At presentation, symptoms and results of laboratory tests were characteristic of acute hepatitis. All patients recovered spontaneously after LipoKinetix use was discontinued. Three of the seven patients, including one who developed fulminant hepatic failure complicated by cerebral edema, were taking LipoKinetix alone at the time of presentation. Of the four patients who were taking multiple supplements, two resumed taking supplements other than LipoKinetix without incident.

Conclusions: The use of LipoKinetix may be associated with hepatotoxicity. Despite extensive evaluations, no other cause for hepatotoxicity could be identified in the seven patients studied.

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See editorial comment on pp 616-618.

Unlike licensed drugs, dietary supplements are not subject to review by the U.S. Food and Drug Administration (FDA) before marketing. Issues pertaining to the use of certain herbal products range from contamination with heavy metals (including lead, arsenic, and mercury) (1–3) to substitution of a product ingredient or misidentification of raw herbs that can result in toxicity (4). Hepatotoxicity has been associated with various herbal products (5, 6).

LipoKinetix (Syntrax, Cape Girardeau, Missouri) capsules are sold as a dietary supplement for weight loss. In the United States, $33 billion is spent yearly on weight-loss products and services (7), despite the absence of scientific evidence in humans to support such use (8). According to the manufacturer, the purported mechanism of action of LipoKinetix is "modifying a process in the body called oxidative phosphorylation" that thereby "mimics exercise." LipoKinetix contains the following ingredients: norephedrine hydrochloride (25 mg), sodium usniate (100 mg), 3,5-diiodothyronine (100 μg), yohimbine hydrochloride (3 mg), and caffeine (100 mg). We describe seven patients who between July and December 2000 developed acute hepatitis, including one patient who developed fulminant hepatic failure complicated by cerebral edema, after ingesting LipoKinetix.

CASE SERIES

Five patients (four women and one man) were treated at Cedars-Sinai Medical Center, Los Angeles, California, and two patients (both men) were identified through the FDA MedWatch program. All seven patients had taken LipoKinetix according to the manufacturer's recommendations, and none were taking prescription or over-the-counter medications (including acetaminophen). No patient had a medical history, and none were obese. Results of serologic testing for hepatitis A, B, and C were negative in all patients. Results of autoimmune serologic testing (for antinuclear antibodies and anti–smooth-muscle antibodies) and results of testing for cytomegalovirus and Epstein–Barr virus were also negative in five patients who were tested. The five patients from Cedars-Sinai Medical Center were Japanese nationals residing in the Los Angeles area. They had purchased different lot numbers of the product at the same health food store. Symptoms appeared within 4 weeks after initial ingestion of LipoKinetix.

The other two patients, identified from the MedWatch program, were white bodybuilders who were acquaintances and had purchased the product through the Internet. They sought medical attention at 9 and 12 weeks, respectively, after first taking LipoKinetix. It is

Context

Dietary supplements, unlike drugs, are not tightly controlled by the U.S. Food and Drug Administration (FDA) before marketing.

Contribution

LipoKinetix, a dietary supplement sold as an aid to promote weight loss, was associated with severe hepatotoxicity in seven previously healthy patients. None had evidence of viral infection or autoimmune disease or had ingested other hepatotoxic drugs. All patients recovered spontaneously after discontinuing use of LipoKinetix.

Implications

Although the FDA has issued warning letters to the manufacturer, physicians, and the public regarding LipoKinetix, federal oversight of dietary supplements remains problematic. Physicians should inquire about the use of dietary supplements when patients present with evidence of hepatotoxicity.

–The Editors

unclear whether the lot numbers of the product used by these two patients differed. The clinical summary is presented in **Table 1**. Three of the seven patients, including the patient who developed fulminant hepatic failure, were taking only LipoKinetix at the time symptoms occurred (**Table 2**). Two of the four patients taking multiple supplements subsequently resumed taking supplements other than LipoKinetix without incident.

CASE REPORT

A previously healthy, 20-year-old female Japanese exchange student began taking LipoKinetix for weight loss 2 weeks before presenting with a low-grade fever, malaise, and worsening epigastric pain. She had jaundice, was alert and oriented, and did not have hepatosplenomegaly. Laboratory studies revealed an aspartate aminotransferase level of 49.64 μkat/L (2978 U/L), alanine aminotransferase level of 47 850 nkat/L (2871 U/L), total bilirubin level of 222 μmol/L (13.0 mg/dL), and international normalized ratio of 2.8. Aminotransferase levels continued to increase and peaked 5 days after the patient discontinued taking LipoKinetix. The patient became increasingly coagulopathic and developed stage 2 hepatic encephalopathy. She was evaluated for liver transplantation. With the subsequent development of stage 3 encephalopathy, the patient was intubated. Intracranial pressure was 35 mm Hg, and mannitol was administered. The intracranial pressure decreased with supportive care, and liver function test results improved over the next 6 days. On discharge, she had no neurologic sequelae and the international normalized ratio was normal. Aminotransferase levels returned to normal within 12 weeks.

ANALYSIS

Three different lot numbers of LipoKinetix capsules were obtained from three patients treated at Cedars-Sinai Medical Center. The FDA analyzed these samples at Pacific Regional Laboratory SW (Los Angeles, California) using liquid chromatography–electrospray mass spectrometry and Fourier transform infrared spectroscopy. Analyses confirmed that the product samples contained norephedrine, yohimbine, 3,5-diiodothyronine, sodium usniate (analyzed as usnic acid), and caffeine, as listed on the product label. No contaminants (including heavy metals) were detected.

DISCUSSION

Unlike with licensed drugs, the safety of herbal products has relied on their traditional use and formulations for appropriate dosage, administration, and avoidance of harmful interactions. The dietary supplement market is a multibillion-dollar industry; use of herbal products has increased an estimated 380% from 1990 to 1997 (9). Competition has driven dietary supplement manufacturers to seek obscure ingredients and to use them in nontraditional ways and combinations.

We report on seven healthy people who were not taking any prescription drugs and developed severe hepatotoxicity while taking LipoKinetix. All patients had used the manufacturer's recommended dosages. Five patients had taken the supplement for 1 month or less, and two patients had used the product for 2 to 3 months. All presented with symptoms characteristic of acute hepatitis, including fatigue and abdominal pain. In addition, results of biochemical testing were consistent with acute hepatitis. The peak aminotransferase levels and pattern of liver test results were compatible with drug-induced acute hepatocellular necrosis. There was no evidence of allergy, such as rash or eosinophilia. Three patients developed significant jaundice, and one developed fulmi-

Table 1. **Patient Characteristics***

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age, *y*	20	32	31	28	23	26	31
Sex	Female	Female	Male	Female	Female	Male	Male
Duration of LipoKinetix use, *d*	14	10	30	30	21	84	63
Jaundice	Yes	Yes	Yes	No	No	Yes	Yes
Abdominal pain	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nausea or vomiting	No	Yes	No	Yes	Yes	No	No
Peak AST level, *µkat/L (U/L)*	49.64 (2978)	156.03 (9360)	23.27 (1396)	34.47 (2068)	63.78 (3826)	125.86 (7550)	9.40 (564)
Peak ALT level, *nkat/L (U/L)*	47 850 (2871)	117 335 (7040)	7300 (438)	34 784 (2087)	63 767 (3826)	235 838 (14 150)	18 317 (1099)
Peak bilirubin level, *µmol/L (mg/dL)*	250 (14.6)	197 (11.5)	79 (4.6)	67 (3.9)	38 (2.2)	104 (6.1)	41 (2.4)
Ethnicity	Japanese	Japanese	Japanese	Japanese	Japanese	White	White
Medical history	None	None	None	None	None	None	None
Required hospitalization	Yes	Yes	Yes	No	No	No	No
Other product use (see Table 2)	No	Yes	Yes	Yes	No	Yes	No
Time between starting LipoKinetix and onset of symptoms, *d*	14	10	30	30	21	84	63
Time between discontinuing LipoKinetix and normalization of aminotransferase levels, *d*	84	84	28	70	Improving after 7 days; declined further follow-up	90	Symptoms resolved after 60 days; declined further follow-up
Resumed using supplements other than LipoKinetix without incident	NA	No	Yes	No	NA	Yes	NA

*ALT = alanine aminotransferase; AST = aspartate aminotransferase, NA = not available.

nant hepatic failure. All recovered spontaneously after discontinuing use of LipoKinetix, and results of liver tests as well as symptoms normalized within 4 months in five patients (two patients declined to have further testing). No other hepatotoxic agent or other cause for hepatotoxicity could be identified. Of the four patients taking multiple supplements, only one had taken multiple Chinese herbal formulations; however, none of the ingredients were associated with hepatotoxicity according to the Chinese *Materia Medica*, the standard reference for Chinese herbs (10).

LipoKinetix-induced hepatotoxicity appears to be idiosyncratic (5, 11, 12). No published reports have described hepatotoxicity associated with any of the other individual substances contained in LipoKinetix. *Ephedra* alkaloids have been associated with multiple adverse cardiovascular and central nervous system events (13). Only a single reported case of acute hepatitis has been associated with *Ephedra*; however, that patient had taken numerous other products (14). The FDA notes relatively few cases of hepatitis or elevated aminotransferase levels associated with dietary supplements containing ephedrine alkaloids (approximately 25 of 1400 cases). These adverse event reports are often complex, with patients concurrently using many other products (dietary supplements and drugs), some of which have known hepatotoxic effects. Although a direct hepatotoxic effect has not been reported for ephedrine or norephedrine

Table 2. **Supplements: Use and Duration***

Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
LipoKinetix, 2 wk	LipoKinetix, 10 d	LipoKinetix, 4 wk	LipoKinetix, 4 wk	LipoKinetix, 3 wk	LipoKinetix, 12 wk	LipoKinetix, 9 wk
	Flaxseed oil, 10 d	Ripped Fuel (contains *Ephedra*), 1 y	QualiHerb: Ginseng and Zizyphus Formula, 4 wk		Myoplex, Myoplex Deluxe, and HMB, 6 mo	
	Pyruvate, 10 d	Thermbuterol, 1 y	Yao San #21124 TB, 4 wk		Creatine, 6 mo	
	Chitosan, 10 d	Yellow Jacket (contains *Ephedra*), 1 y	Lotus Herb: Gui Pi Tang–Ginseng and Longan Combination, 4 wk		Animal Pak, 6 mo	

* Ingredients contained in each supplement are described in the Appendix.

(also a metabolite of ephedrine), phenylpropanolamine (racemic norephedrine) has been reported to potentiate the hepatotoxicity of carbon tetrachloride and acetaminophen in mice (6, 15).

Sodium usniate, the salt form of usnic acid, is a secondary metabolite found in several genera of lichens, including *Usnea*, *Letharia*, and *Parmelia*. Toxic reactions, including ataxia leading to paralysis and death, have been reported in animals ingesting lichens containing usnic acid; data in humans, however, are limited. Usnic acid uncouples oxidative phosphorylation in murine liver mitochondria, resulting in inhibition of adenosine triphosphate synthesis and enhancement of Mg^{2+}-adenosine triphosphate activity, which may contribute to hepatic toxicity (16). None of the seven patients, however, exhibited lactic acidosis, a typical feature of drug-induced liver injury due to mitochondrial dysfunction.

Yohimbine is an indole alkaloid from the bark of the African *Pausinystalia yohimbe* tree and is also found in *Rauwolfia* root (17). The FDA has not evaluated yohimbine for safety or efficacy for any indication. It is widely touted as a remedy for male impotence, but the mode of action is by selective blockade of the presynaptic α_2-receptor (17). Yohimbine penetrates the central nervous system and can stimulate mood and motor activity (17). Nausea, vomiting, abdominal pain, dizziness, and headache have been reported when yohimbine is used at therapeutic doses (17).

Unintentional thyrotoxicosis factitia, a condition related to ingestion of exogenous thyroid hormone from adulterated products (for the purpose of weight loss) is well described (18). None of the seven patients exhibited clinical signs of hyperthyroidism, and abnormal liver tests results in these seven patients were not typical of the pattern of hepatic dysfunction seen in hyperthyroidism (19).

Although a hepatotoxin was not identified in LipoKinetix, many mechanisms could be responsible for the observed hepatotoxicity. These include toxic effects related to interactions of the ingredients in the product, such as the potentiation (noted earlier) between phenylpropanolamine (norephedrine) and acetaminophen or carbon tetrachloride. Various factors may explain these interactions, including the induction of certain enzymes or formation of secondary toxic metabolites due to alterations in pharmacokinetic and pharmacodynamic properties of certain ingredients. Alternatively, pharmacogenetic predisposition may contribute to LipoKinetix-induced hepatotoxicity.

Dietary supplement products are not subject to review by the FDA before marketing. The current system for monitoring herbal products relies on the voluntary reporting of any serious adverse events by physicians. This case series highlights the need for public and medical community awareness that some supplements may contain ingredients in combinations and at doses not previously used. Patients often do not disclose information on supplement use; this underscores the need for a responsible dialogue between physicians and patients about all health-related products (including botanicals and supplements) being used by the patient (7) and the timely reporting of all adverse events to public health agencies. We refer readers to the MedWatch Web site www.fda.gov/medwatch/report/hcp.htm) and telephone number (800-FDA-1088).

APPENDIX: INGREDIENTS IN DIETARY SUPPLEMENTS

Flaxseed Oil (multiple manufacturers): Linolenic, linoleic, and oleic acids.

Chitosan (multiple manufacturers): Shellfish fiber.

Twinlab Ripped Fuel (Twin Laboratories, Ronkonkama, New York): Chromium picolinate, 200 μg; Mahuang extract (standardized for 20-mg ephedra alkaloids), 334 mg; guarana seed extract (standardized for 22% caffeine), 910 mg; L-carnitine, 100 mg; gelatin; cellulose; purified water; MCT; silica; and magnesium stearate.

Thermbuterol (Alternative Pharmaceuticals, Roselle, New Jersey): *Sida cordifolia*; synephrine; guarana (contains caffeine); guggulsterone; L-carnitine; and white willow bark, 650 mg.

Yellow Jacket (NVE Pharmaceuticals, Newton, New Jersey): Ephedra extract, *Sida cordifolia*, *Citrus aurantium* (standardized for 4% synephrine), kola nut, ginseng, ginger root, and *Capsicum*.

QualiHerb: Ginseng and Zizyphus Formula (Sheng Chang Pharmaceuticals, Bentley Place Cerritos, California): Rehmanniae, ginseng, Polygalae, *Acori graminei*, Scrophulariae, Biotae, Blatycodi, Asparagi, *Salviae miltiorrhizae*, *Zizyphus spinosae*, Ophiopogonis, Coptidis, Pararadicis Poriae, *Angelicae sinensis*, and Schisandrae.

Yao San #21124 TB: Chai Hu, Bupleuri, Dang Gui, *Angelicae sinensis*, Bai Zhu, *Atractylodis alba*, Shong Jiang, Zingiberis, Bo He, Menthae, Bai Shao, *Paeoniae alba*, Fu Ling, Poriae Cocos, Gan Cao, and Glycyrrhizae.

Lotus Herb: Gui Pi Tang—Ginseng and Longan Combination: Ren Shen, Gwsong, Bai Zhu, *Atractylodis*, Fu Ling, Poriae, Suan Zao Ron, Zizyphus seeds, Long Yan Rou, Longan, Huang Q, *Astragali*, Dang Gui, Tangkuei, Yuan Zhi, Polygalae, Mu Xiang, Saussurea, Gan Cao, licorice, Shong Jiang, ginger, Da Zao, and red jujube.

Myoplex (Experimental and Applied Sciences, Inc., Golden, Colorado): MyoPro (unique blend of whey-protein concentrate from specially filtered and ion-exchanged whey protein, calcium caseinate, milk-protein isolate, taurine, L-glutamine, sodium caseinate, egg albumin, and calcium α-ketoglutarate), maltodextrin, corn syrup solids, vitamin and mineral blend (potassium chloride, disodium phosphate, magnesium oxide, calcium phosphate, potassium citrate, potassium phosphate, choline bitartrate, β-carotene, ascorbic acid, DL-α-tocopheryl acetate, ferrous fumarate, molybdenum amino acid chelate, boron proteinate, manganese gluconate, selenium amino acid chelate, niacinamide, zinc oxide, D-calcium pantothenate, chromium citrate, copper sulfate, vitamin A palmitate, pyridoxine hydrochloride, riboflavin, thiamin hydrochloride, vitamin D_3, folic acid, biotin, potassium iodide, and cyanocobalamin), aspartame, CitriMax (garcinia cambogia), Dutch processed cocoa, natural and artificial flavor, partially hydrogenated canola oil, salt, medium-chain triglycerides, xanthan gum, soy lecithin, monoglycerides and diglycerides, cellulose gum, and borage oil.

Myoplex Deluxe (Experimental and Applied Sciences, Inc., Golden, Colorado): MyoPro (proprietary protein blend containing whey-protein isolate from ion exchanged whey, milk-protein isolate, calcium caseinate, sodium caseinate, and egg albumin), maltodextrin, GKG (proprietary blend containing L-glutamine, calcium α-ketoglutarate, taurine, potassium chloride, potassium phosphate, magnesium phosphate, magnesium oxide, sodium RNA, and manganese glycinate), natural and artificial flavors, Dutch processed cocoa, CLA (calcium conjugated linoleic acid from sunflower oil), partially hydrogenated canola oil, xanthan gum, V2G (proprietary blend containing taurine, vanadyl sulfate, and sodium selenate), vitamin and mineral blend (choline bitartrate, β-carotene, ascorbic acid, DL-α-tocopheryl acetate, ferrous fumarate, molybdenum amino acid chelate, boron proteinate, niacinamide, zinc oxide, calcium pantothenate, chromium citrate, copper sulfate, vitamin A palmitate, pyridoxine hydrochloride, riboflavin, thiamin hydrochloride, vitamin D_3, folic acid, biotin, potassium iodide, and cyanocobalamin), corn syrup solids, salt, soy lecithin, aspartame, cellulose gum, carrageenan, CitriMax (*Garcinia cambogia*), medium-chain triglycerides, monoglycerides and diglycerides, and borage oil.

HMB (multiple manufacturers): Calcium β-hydroxy β-methylbutyrate monohydrate.

Animal Pak (Universal Nutrition, Inc., New Brunswick, New Jersey): Vitamin A acetate, β-carotene, ascorbic acid, ergocalciferol, thiamin HCl, riboflavin, niacin, pyridoxin HCl, folic acid, calcium pantothenate, biotin, citrate, carbonate, calcium phosphate, kelp, magnesium oxide, zinc oxide, selenium, copper sulfate, manganese sulfate, chromium picolinate, potassium sulfate, lactalbumin, Siberian ginseng (from root), Oriental ginseng (from root), *Smilax officinalis* (from root), protogen A, inosine, pyridoxine α-ketolutarate, L-carnitine, coenzyme A, coenzyme B-12, phosphatidylcholine, para-aminobenzoic acid, bovine colostrum, bovine Argentine liver, shark cartilage, choline complex, bioflavonoids, linoleic acid, oleic acid, betaine HCl, pepsin, papain, ox bile, pancreatin, mycozyme, maltodextrin, calcium sulfate, magnesium stearate, choline citrate, stearic acid, parsley, goldenseal, don quai, burdock, alfalfa, water cress, rice bran, cellulose, and rose hips.

From Cedars-Sinai Medical Center, Burns and Allen Research Institute, University of California, Los Angeles, School of Medicine, Los Angeles, California; and Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, D.C.

On 19 November 2001, the U.S. Food and Drug Administration released a letter to health care professionals (www.cfsan.fda.gov/~dms/ds-ltr25.html) that contained the following sentence: "We urge you to review your cases of hepatitis in order to determine if any may be related to the use of dietary supplements in these patients."

–The Editors

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Potential Physician Malpractice Liability Associated with Complementary and Integrative Medical Therapies

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Physicians are increasingly grappling with medical liability issues as complementary and integrative health care practices are made available in conventional medical settings. This article proposes a framework in which physicians can assess potential malpractice liability issues in counseling patients about complementary and integrative therapies. The framework classifies complementary and integrative therapies according to whether the evidence reported in the medical and scientific literature supports both safety and efficacy; supports safety, but evidence regarding efficacy is inconclusive; supports efficacy, but evidence regarding safety is inconclusive; or indicates either serious risk or inefficacy. Clinical examples in each category help guide the clinician on how to counsel patients regarding use of complementary and alternative medical therapies in a given clinical situation. Specific strategies to reduce the risk for potential malpractice liability include the following: 1) determine the clinical risk level; 2) document the literature supporting the therapeutic choice; 3) provide adequate informed consent; 4) continue to monitor the patient conventionally; and 5) for referrals, inquire about the competence of the complementary and alternative medicine provider. This framework provides a basis for clinical decisions involving complementary and integrative care.

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In the late 19th century, scientific medicine (or biomedicine) came to dominate U.S. professional health care, as well as legal and regulatory structures governing health care (1). By the mid-20th century, popular interest in therapies such as acupuncture and massage therapy led to the growth of "alternative medicine," denoting therapies not commonly used in U.S. hospitals or taught in U.S. medical schools (2). With increasing emphasis on these therapies among hospitals, medical schools (3), and consumers (4), "complementary and alternative medicine" (CAM) came to describe therapies historically outside of biomedicine, and "complementary and integrative care" came to describe the clinical integration of biomedicine and CAM. We review legal rules relevant to potential malpractice liability for complementary and integrative care, propose a framework in which physicians can assess liability risk, and offer specific strategies for liability management. We first address the counseling of patients regarding CAM therapies and then discuss the referral of patients to CAM providers.

COUNSELING OR OFFERING CAM THERAPIES

The legal standard for malpractice liability is whether a given therapy falls below the standard of care and thereby injures the patient (5). Standards of care in the medical profession develop through the interaction of medical leaders, professional journals and meetings, and peer networks and are proven by expert medical testimony at trial (5). Because the field of complementary and integrative care is emerging (6), the standards of care tend to be less developed than in conventional medicine. Therefore, courts assessing whether the standard of care has been met and whether the therapy has harmed the patient are likely to rely on medical consensus regarding the safety and efficacy of a given CAM therapy. Likewise, physicians reviewing the integration of CAM therapies into conventional care should determine the extent to which the evidence reported in the scientific and medical literature supports both safety and efficacy (**Figure**, *panel A*); supports safety, but evidence regarding efficacy is inconclusive (**Figure**, *panel B*); supports efficacy, but evidence regarding safety is inconclusive (**Figure**, *panel C*); and indicates either serious risk or inefficacy (**Figure**, *panel D*).

Standards of care change over time as medical research determines the extent to which given CAM therapies are safe or effective; therefore, a given therapy may change its position in the spectrum of clinical risk just outlined. This is true for all medical interventions regardless of their origin—allopathic or complementary. Furthermore, to a jury, there may be a meaningful distinction between the physician who initiates the CAM therapy or referral to a CAM provider and the physician who responds to a patient's choice of, or request for advice regarding, a CAM therapy. Nonetheless, reasoned judgments concerning clinical risk in each cate-

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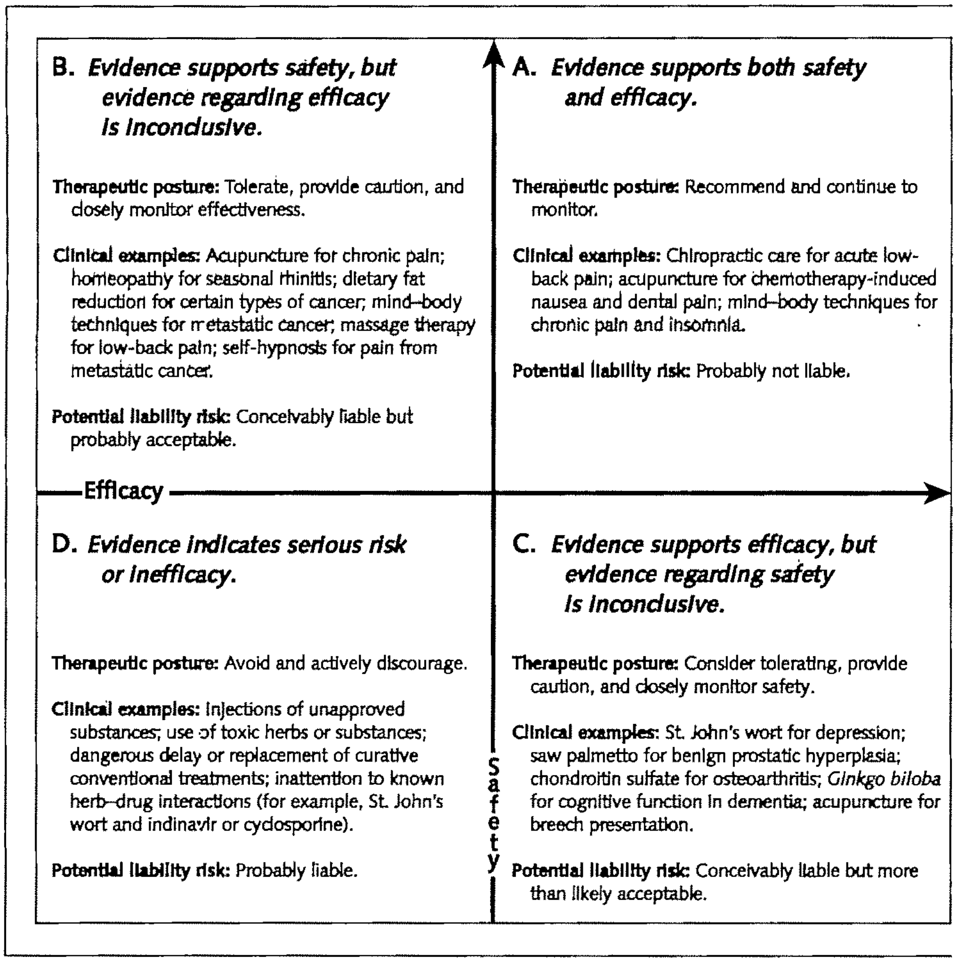
Figure. **Potential malpractice liability risk associated with complementary and integrative medical therapies.**



B. ***Evidence supports safety, but evidence regarding efficacy is inconclusive.***

Therapeutic posture: Tolerate, provide caution, and closely monitor effectiveness.

Clinical examples: Acupuncture for chronic pain; homeopathy for seasonal rhinitis; dietary fat reduction for certain types of cancer; mind–body techniques for metastatic cancer; massage therapy for low-back pain; self-hypnosis for pain from metastatic cancer.

Potential liability risk: Conceivably liable but probably acceptable.

A. ***Evidence supports both safety and efficacy.***

Therapeutic posture: Recommend and continue to monitor.

Clinical examples: Chiropractic care for acute low-back pain; acupuncture for chemotherapy-induced nausea and dental pain; mind–body techniques for chronic pain and insomnia.

Potential liability risk: Probably not liable.

D. ***Evidence indicates serious risk or inefficacy.***

Therapeutic posture: Avoid and actively discourage.

Clinical examples: Injections of unapproved substances; use of toxic herbs or substances; dangerous delay or replacement of curative conventional treatments; inattention to known herb–drug interactions (for example, St. John's wort and indinavir or cyclosporine).

Potential liability risk: Probably liable.

C. ***Evidence supports efficacy, but evidence regarding safety is inconclusive.***

Therapeutic posture: Consider tolerating, provide caution, and closely monitor safety.

Clinical examples: St. John's wort for depression; saw palmetto for benign prostatic hyperplasia; chondroitin sulfate for osteoarthritis; *Ginkgo biloba* for cognitive function in dementia; acupuncture for breech presentation.

Potential liability risk: Conceivably liable but more than likely acceptable.

gory can help physicians to assess potential liability risk when counseling patients about CAM therapies.

Evidence Supports Both Safety and Efficacy

Once evidence supports both safety and efficacy, the CAM therapy should gain general medical acceptance, fall within the standard of care (1), and, by definition, present little risk for patient injury (7). Therefore, the physician who provides or counsels a patient under his or her care about such a therapy is *probably not liable* in malpractice. Furthermore, if the evidence supports both safety and efficacy, the physician should *recommend yet continue to monitor* these CAM therapies. Clinical examples in this region are those for which the National Institutes of Health has published a clinical practice guideline or a consensus or assessment statement—namely, chiropractic for acute low back pain (8, 9), acupuncture for chemotherapy-induced nausea and dental pain (10), and mind–body techniques for chronic pain and insomnia (11) (**Figure**). To the extent that the therapy is not only safe and effective but also highly cost-effective, it also may be considered nonexperimental and medically necessary, and thus appropriate for third-party reimbursement.

Evidence Supports Safety, but Evidence Regarding Efficacy Is Inconclusive

If evidence supports safety but evidence regarding efficacy is inconclusive, the therapy might fall below the standard of care yet not injure patients. Therefore, while the physician is *conceivably liable,* use of the therapy is *probably acceptable.* The physician should *tolerate, pro-*

vide caution, and closely monitor effectiveness for these therapies. The physician's recommendations and discussions with the patient should be documented in the patient's medical record.

As examples, massage, homeopathy, mind–body techniques, dietary fat reduction, and acupuncture are rarely associated with clinically significant adverse events, but evidence for their efficacy generally is inconclusive (for example, adverse events associated with acupuncture have occurred, but only rarely [12–15]). Situations in which the medical literature shows potential clinical efficacy include acupuncture for the treatment of chronic pain (16), homeopathy to treat seasonal rhinitis (17), dietary fat reduction in women with breast cancer (18, 19), mind–body techniques for patients with metastatic breast cancer (20), massage therapy to treat low-back pain (21), and self-hypnosis as an adjunctive treatment for pain associated with metastatic cancer (22). From an ethical perspective, as the evidence of safety of the CAM treatment strengthens, the physician's acceptance of its use becomes more appropriate (23). This assumes that CAM use has not indirectly harmed the patient by 1) replacing necessary conventional care (for example, by relying exclusively on mind–body techniques for patients with cancer and thus delaying or forgoing necessary surgery) (7, 24) or 2) necessitating out-of-pocket resources for unproven medical interventions (24).

Evidence Supports Efficacy, but Evidence regarding Safety Is Inconclusive

If evidence supports efficacy but evidence regarding safety is inconclusive, the therapy could be viewed as the cause of any subsequent patient injury; thus, in such situations, the physician is *conceivably liable.* On the other hand, in the absence of an efficacious biomedical treatment, respecting the patient's decision to try a CAM therapy becomes more ethically appropriate as the evidence of its efficacy grows (23). Assuming that the therapy presents a relatively low level of danger, its inclusion in treatment is *more than likely acceptable* in terms of potential liability risk.

Many herbs potentially fall in this category—for example, the use of St. John's wort for certain types of depression (25), saw palmetto for uncomplicated benign prostatic hyperplasia (26), chondroitin sulfate for osteoarthritis (27), and *Ginkgo biloba* for cognitive function in dementia (28, 29). However, quality control of herbal products is not guaranteed by Food and Drug Administration standards and may vary considerably (30). A nondietary supplement example is moxibustion for use in breech presentation (31). Given the present limits of scientific knowledge concerning drug–herb interactions (32–35) and the mechanism for therapies such as moxibustion (especially for conditions such as breech presentation), as well as the physician's inability to ensure quality control (for example, that an herbal product contains what it purports to contain), the physician should *consider tolerating, provide caution, and closely monitor safety* associated with these therapies for these conditions.

Evidence Indicates Either Serious Risk or Inefficacy

From a liability standpoint, by pursuing a therapy for which evidence indicates either inefficacy or serious risk, the physician is not only deviating from conventional standards of care but also causing patient injury; thus, the physician is *probably liable.* This scenario may trigger concerns about professional conduct and competence, creating the additional possibility of a professional disciplinary proceeding and revocation of licensure (1). Clinical examples include the injection (intravenous or intramuscular) of unapproved substances; the use of herbs known to be directly toxic (for example, chaparral [36] and *Aristolochia fangchi* [37]); substances proven ineffective in randomized, controlled trials (such as laetrile) (38, 39); clinical use of herbs known to be associated with clinically significant drug–herb interactions (32–34); or knowing use of a CAM therapy that delays treatment for a potentially curable condition—for example, delay of recommended lumpectomy and radiation therapy in favor of adopting a macrobiotic diet for a patient with stage I breast cancer. The physician should *avoid and actively discourage* pursuit of such treatments. If the patient insists on pursuing the treatment, the physician should document the discussion, including his or her disclosure to the patient of evidence regarding documented or potential dangers and any proven lack of efficacy, if such data exist.

EVALUATING SAFETY AND EFFICACY OF CAM THERAPIES

In evaluating safety and efficacy, the physician should review the available scientific and medical literature regarding the proposed CAM therapy. Present medical consensus provides a basis for decision making in the clinical scenarios outlined above. Continually emerging research, however, makes conclusive judgments difficult and renders even the above choices amenable to interpretation by individual clinicians. One possibility is to fashion evaluative criteria for safety and efficacy based on requirements such as 1) the existence of sufficient (quantity and quality of) randomized, controlled trials (either alone or in combination with a meta-analysis) supporting efficacy (or lack thereof) and 2) the existence (or lack thereof) of documented, major (for example, life-threatening or permanently disabling) adverse events associated with the therapy or obvious, theoretical potential (or lack thereof) for major adverse events occurring in association with the therapy (Weiger WA, Smith M, Boon H, Richardson MA, Kaptchuk TJ, Eisenberg DM. Advising patients with cancer who seek complementary/alternative/integrative medical therapies: an evidence-based approach. Submitted for publication). Such criteria are necessarily in flux and will change over time as new CAM research continues to emerge.

LIABILITY MANAGEMENT STRATEGIES (COUNSELING OR OFFERING CAM THERAPIES)

The strategies below suggest steps physicians can take to help minimize potential malpractice liability risks when counseling patients about CAM therapies.

1. *Determine the clinical risk level.* Review existing medical literature to assess the evidence for safety and efficacy of a given CAM therapy, such that a medical expert could testify and convince the jury that use of the therapy met the standard of care and did not injure the patient. Among other resources, the Cochrane Collaboration maintains an updated international database of clinical trials involving CAM therapies (40). Furthermore, resources exist on assessing the quality of CAM-related research (41–43).

2. *Document the literature supporting the therapeutic choice.* Poor documentation in the medical record can help demonstrate a failure of due care and justify discipline by a state medical board. On the other hand, documentation in the medical record, including a back-up file of literature supporting safety and efficacy, can help protect the physician against unwarranted medical board action (44). Consider peer review of clinically riskier choices—for example, prior consideration by an appropriate hospital committee of permissible herbs and practice guidelines for use of such herbs. If the institution does not have or does not plan to create such a committee, discuss the therapeutic choice with colleagues and document any formal or informal institutional approval.

3. *Provide adequate informed consent by engaging in a clear discussion of the risks and benefits of using the CAM therapy.* Whenever possible, provide a discussion of the known risks and benefits of the CAM therapy, together with a discussion of what is not known or cannot be evaluated, as part of the obligation of informed consent (7). Arguably, informed consent also should encompass the risks and benefits of combining conventional care with CAM therapies versus providing conventional care alone (45). Document this disclosure in writing, where appropriate (for example, when the patient is competent and wishes to pursue a CAM therapy associated with documented or potential risk) (45), and especially when the patient elects to proceed with the CAM therapy against medical advice.

4. *If feasible, obtain the patient's express, written agreement to use the CAM treatment.* The legal doctrine of "assumption of risk" states that if a patient knowingly, intelligently, and voluntarily accepts the risks of a treatment provided with due care, the patient's "assumption of risk" relieves the physician of malpractice liability. In *Schneider v. Revici* (46), the patient sought nonsurgical treatment for breast cancer and signed a consent form releasing her physician from liability. The court held that if the patient had "made an informed decision to go outside currently approved medical methods in search of an unconventional treatment" and thereby had expressly assumed the risk of such treatment, then the physician would have a complete defense to malpractice (47). In *Charell v. Gonzales*, a New York state court held that a patient had "impliedly" assumed the risk that the CAM therapy would fail, because the patient "did a significant amount of investigation . . . and hence became quite knowledgeable on the subject" and "sought to avoid the suffering that accompanied the chemotherapy/radiation regimen" (48). The patient was found 49% responsible, and the physician's liability was reduced accordingly.

Although the legal distinction between "express" and "implied" assumption of risk varies by state (7, 49), the *Schneider* and *Charell* cases suggest that patient initiation of, interest in, or stated acceptance of a CAM therapy may affect liability. Furthermore, the physician may have a defense to malpractice if 1) the patient expresses consent (preferably in writing) to try the specific CAM therapy (1, 7, 49), 2) the physician has therapeutic justification for selecting that therapy, and 3) the physician exercises due care in delivering the therapy (50). The physician should request documentation if the liability risk is more than minimal, the patient agrees, and the request does not unduly disrupt the therapeutic relationship.

5. *Continue to monitor the patient conventionally.* Continuing conventional monitoring and follow-up will help to prevent the patient from becoming diverted from necessary conventional therapy, from pursuing useless or harmful treatments, or from deteriorating in situations in which conventional diagnostic or interventional tools may have preserved patient health (24). This is arguably the most important element in advising patients who use, seek, or demand CAM therapies (24); such monitoring and follow-up also help to reduce liability risk. Indeed, in imposing liability in *Charell*, the jury found that the patient was dissuaded from undertaking conventional treatment for uterine cancer (48).

APPLICATION OF LEGAL RULES GOVERNING REFERRALS

Although counseling patients can include referrals to CAM providers, malpractice liability rules involving physician referrals to providers differ from those that apply when the patient is under the physician's care. Referrals can generate direct liability (the decision to refer was itself considered negligent, resulting in patient injury) and vicarious liability (the referring physician becomes legally responsible for the treating practitioner's negligence) (51). Courts are expected to apply the same legal rules to referrals to licensed CAM providers who—like physician specialists or allied health providers, such as physical therapists—deliver independent professional services in a scope of practice circumscribed by state law, based on education and training mandated by the state. Yet, just as courts have been unpredictable in either extending or limiting liability in referrals to conventional providers (7, 51), physicians should understand that the legal landscape is subject to change.

On the basis of existing legal rules, a physician referral to a CAM provider could be considered a "negligent" decision to refer if it delays or eliminates the patient's opportunity to obtain necessary biomedical treatment (51). For example, if the patient has a progressive neurologic deficit and the patient's condition is deteriorating, referring the patient to a chiropractor (without continuing necessary conventional care) could constitute a failure to exercise appropriate medical judgment and thus negligence. A second scenario involves referral to a CAM provider in which the physician "knows or has reason to know" that either the provider or the therapy the provider intends to employ is dangerous (7). For example, referral to a provider of traditional oriental medicine who is known in the community to use intramuscular injections of dried human placenta or extracts of rhinoceros horn might be considered negligent.

Vicarious liability for referral in conventional care has arisen in three scenarios: the referring physician supervised the treating practitioner's care, engaged in joint treatment, or referred the patient to a "known incompetent" (51). First, where statutes or board regulations for specific CAM providers require that physicians supervise the designated CAM providers, physicians could be vicariously liable for such providers' conduct (51). One example involves state statutes requiring physician referral before an acupuncturist can see the patient for treatment of serious conditions, such as cardiac conditions and acute abdominal symptoms (52).

Second, in extending vicarious liability to physicians engaged in a "joint undertaking" with treating practitioners (for example, in our scenario, a multidisciplinary group practice of integrative care), courts have considered whether the physician and practitioner have "acted in concert"—for example, by simultaneously administering treatment. The differences between conventional and CAM diagnostic as well as treatment methods may require a high degree of coordination and communication between the referring physician and the treating provider. Moreover, because the flow of diagnostic and treatment information between physician and CAM providers in the same hospital, health plan, corporation, jointly owned or operated clinic, or an integrated unit in a hospital or clinic may be significant on an institutional level, judges could decide that a joint undertaking has occurred, and thus hold physicians and CAM providers vicariously liable for each other's acts (51). This has considerable implications for the various models of integrative care that currently are being developed at hospitals, health maintenance organizations, and large group practices.

Third, vicarious liability for referral to a "known incompetent" applies if the referring physician knows or should know that the treating practitioner engages in unsafe practices. Possible examples include referral to a treating practitioner who uses unsterilized acupuncture needles or has been professionally disciplined for providing toxic herbs to patients, or referral to a chiropractor known to have an extensive history of malpractice liability for using excessive force on patients. Other examples might include situations in which the referring physician knows or should have known that the CAM provider has graduated from a school that is not accredited by the provider's own professional accrediting organization or that the provider fails to meet professional standards required for hours of education and training.

LIABILITY MANAGEMENT STRATEGIES (REFERRAL)

1. *Closely monitor the clinical risk level.* The physician who learns—through contact with the CAM provider, the patient, or through other sources—that the treating CAM practitioner delivers unsafe or ineffective therapies in the patient's therapeutic regimen—should advise the patient to discontinue the therapeutic relationship with the CAM provider. The physician should closely monitor situations in which a CAM provider uses therapies that have tolerable but as yet undetermined levels of safety or efficacy (**Figure**, *panels B* and *C*).

2. *Document the literature supporting the decision to refer.* Good documentation in the medical record, together with a back-up file containing the supporting literature, can help establish that the referral itself was nonnegligent, thus avoiding direct liability.

3. *Provide adequate informed consent by engaging in a clear discussion of risks and benefits of using CAM.* The physician should describe to the patient the recognized benefits and risks of the referral based on available medical literature. Enhancement of communication by disclosing potential clinical risks also can help manage liability risk and the possibility of a malpractice claim based on inadequate informed consent (45).

4. *Document the discussion of the patient's decision to visit a CAM provider.* Documenting the discussion of the patient's decision to visit a CAM provider can help establish that the patient agreed to treatment with the CAM therapies and thus partly shares legal responsibility for the choice of treatment. The physician also should document whether he or she initiated the referral or is comanaging the patient with a CAM provider with whom the patient has initiated care.

5. *Continue to monitor the patient conventionally.* By continuing conventional monitoring, the physician can intervene with necessary conventional care should the patient's condition deteriorate as a result of over-reliance on therapies delivered by the CAM provider.

6. *Inquire about the CAM provider's competence.* As suggested, complementary and integrative care increasingly may result in shared liability between the referring (or comanaging) physician and the treating CAM provider for "joint treatment." At the same time, the less the referring physician knows about a treating CAM practitioner, the greater the risk for malpractice liability for referral to a "known incompetent." Sufficient knowledge about the CAM provider's history and practice can help assure the physician that referral or comanagement will not create unnecessary liability risk. The following minimal steps will help satisfy courts that the physician has been reasonably diligent in determining competence: 1) review (or ask institutional counsel to review) the licensing statute setting forth the CAM provider's scope of practice, 2) understand the health care services the provider generally delivers, and 3) inquire (or ask the patient to inquire) of any relevant licensing board or professional organization regarding the provider's history of disciplinary action or malpractice litigation. The physician comanaging with CAM providers within an institution should look to internal credentialing processes for this information (53).

CONCLUSION

Increased litigation is likely as physicians are increasingly called on to counsel patients about use of CAM therapies or referrals to CAM providers. The framework that we have outlined here provides a preliminary basis for anticipating and managing potential liability risk surrounding such health care practices.

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Chronic Renal Diseases: Renoprotective Benefits of Renin–Angiotensin System Inhibition

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Progression to renal parenchymal damage and end-stage renal disease, which seems to be largely independent of the initial insult, is the final common pathway for chronic, proteinuric nephropathies in animals and humans. The key event is enhanced glomerular capillary pressure; this impairs glomerular permeability to proteins and permits excessive amounts of proteins to reach the lumen of the proximal tubule. The secondary process of reabsorption of filtered proteins can contribute to renal interstitial injury by activating intracellular events, including upregulation of the genes encoding vasoactive and inflammatory mediators. Both interstitial inflammation and progression of disease can be controlled by such drugs as angiotensin-converting enzyme inhibitors, which strengthen the glomerular permeability barrier to proteins and thereby limit proteinuria and filtered protein-dependent inflammatory signals. Clinical data strongly suggest that remission can now be achieved in some patients with chronic renal disease. Because of the current lag time between starting treatment and remission, however, a substantial proportion of patients still progress to end-stage renal disease before renal function begins to stabilize. A multimodal approach that centers on reducing or removing all risk factors associated with the progression of renal disease may decrease the time to remission of the disease for most patients with proteinuric nephropathies.

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Certain renal diseases seen in clinical practice, such as rapidly progressive glomerulonephritis, have a very rapid course that soon leads to irreversible end-stage renal failure caused by complete structural damage. These diseases, however, are rare. The more common nephropathies, which progress more slowly, still evolve to end-stage renal failure. Diabetes mellitus or hypertension can, in some patients, cause renal injury that progresses to renal failure and the need for kidney replacement therapy.

The number of patients requiring kidney replacement therapy in 1997 was 304 083 in the United States, 175 988 in Japan, and 197 721 in Europe. The number of new patients entering kidney replacement programs has increased constantly in the past 10 years and will probably continue to increase. In the United States, 450 000 patients are expected to require treatment for end-stage renal disease by 2005 (1, 2). With so many patients involved, the costs of treatment will become extremely high and prohibitive, and not just for developing countries (3). Thus, efforts must be directed toward stopping renal diseases from progressing to end-stage renal failure.

METHODS

We identified papers mentioned in this review by searching the MEDLINE database from 1966 to 2000. We selected the most relevant articles (original research and reviews) for this topic using the following individual or combined search terms: *progressive chronic nephropathies, proteinuria, clinical trials, experimental models, renal function, ACE inhibitors, angiotensin II receptor blockers, blood pressure, lipid lowering agents, low protein diet,* and *smoke.* Selected articles were published in the most recognized nephrology journals and in general medicine journals with the highest impact factor.

THE PROGRESSIVE NATURE OF RENAL DISEASES

In 1952, Robert Platt (4) reported that when 80% of the renal tissue was removed from rats, the remaining nephrons became hypertrophied as they assumed a volume of work that a normal kidney would never have to perform. This was interpreted as a possible adaptation to compensate for the effects of nephron loss; renal function then progressively deteriorated. In 1982, however, investigators at Brigham and Women's Hospital in Boston, Massachusetts, first presented the concept that progressive deterioration of renal function was the result of compensatory glomerular hemodynamic changes in response to nephron loss related to the original insult; the hemodynamic changes then caused relentless injury of the remaining intact nephrons (5, 6).

In animal models, high intraglomerular capillary pressure impairs the size-selective function of the glo-

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merular permeability barrier and causes protein ultrafiltration (7, 8). In 1986 (9), Bertani and colleagues suggested that proteins filtered through the glomerular capillary wall might have intrinsic renal toxicity and could contribute to the progression of renal damage. Consistent with these experimental observations was evidence that in humans with nephropathy, disease progressed more quickly when proteinuria was more severe (10–13).

Even in normal conditions, proteins cross the glomerular capillary wall in large amounts and return to the blood by a transtubular mechanism involving proximal tubular cells (14, 15) (**Figure 1**). Abundant evidence from in vitro cell culture studies (16–18) and in vivo rat models of proteinuric renal disease (19–25) indicates that reabsorption of filtered proteins activates the proximal tubular epithelium. Biochemical events associated with tubular cell activation in response to protein stress include upregulation of the genes encoding vasoactive and inflammatory substances and synthesis of the corresponding protein products, such as endothelin-1 (16), monocyte chemoattractant protein (MCP-1) (17), and RANTES (regulated upon activation, normal T-cell expressed and secreted) (18, 26).

Inflammatory and vasoactive substances formed in excessive amounts by proximal tubuli are secreted toward the basolateral compartment of the cell and give rise to an inflammatory reaction in the interstitium that consistently precedes renal scarring. These processes can be accelerated by cytokines released by tubular epithelial cells and by inflammatory cells that accumulate in the interstitium when proteinuria is present (27–31).

LIMITING PROTEIN TRAFFIC PREVENTS THE PROGRESSION OF RENAL DISEASE IN ANIMALS

In chronic proteinuric nephropathies, if the interstitial inflammatory reaction and the subsequent fibrosis were indeed a feature of protein overloading, limiting protein traffic or the biological effect of excessive tubular protein reabsorption should prevent or slow the progression of renal disease. This is precisely what happens in animals treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (**Figure 2**). In experimental diabetes, short- or long-term treatment with enalapril or the angiotensin II receptor blocker losartan reduced proteinuria and conferred protection (32, 33). Use of ACE inhibitors reduced proteinuria and limited progressive deterioration of renal function in other models of renal disease, including spontaneous proteinuria in aging male Munich Wistar Fromter/Ztm rats (34) and rats with passive Heymann nephritis (35), an experimental model that mimics membranous nephropathy in humans.

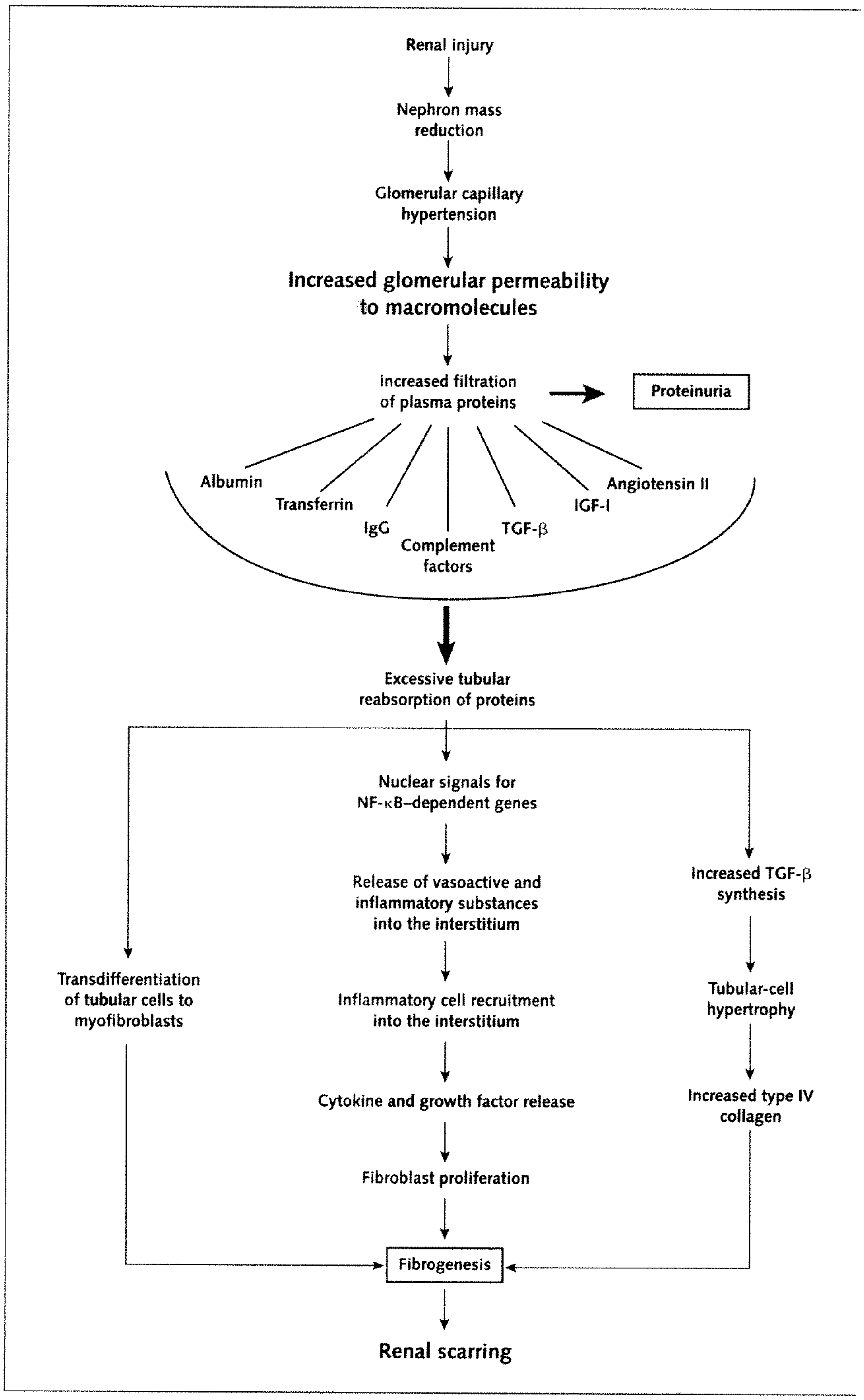
In a recent study of rats with Heymann nephritis and severe proteinuria, simultaneous blocking of angiotensin II and endothelin-1 activity by an ACE inhibitor, together with an endothelin type A receptor antagonist, was more renoprotective than either drug alone (36). Thus, in animals, limiting protein excretion and the resulting activation of tubular epithelial cells is instrumental in protecting the kidney from further damage.

FROM ANIMAL EXPERIMENTS TO DESIGNING A CLINICAL STUDY

Clinical studies and clinicopathologic correlations in patients with progressive proteinuric nephropathies indicate that the observations in experimental models are relevant to understanding human disease (37). Among several baseline measures, proteinuria was a strong and independent predictor of renal outcome in a series of 840 patients with nondiabetic renal disease entering the Modification of Diet in Renal Disease (MDRD) study (38) and in 409 patients with type 1 diabetes and nephropathy (39). Moreover, in patients with nephroangiosclerosis (40), the onset of de novo proteinuria after years of stable renal function indicated subsequent decline in renal function.

Minimal-change disease seems to be an exception to the rule that interstitial infiltrates develop with time in proteinuric glomerulopathies. This type of disease is the only example of a human proteinuric nephropathy in which a substantial percentage of patients consistently respond to steroids. Thus, periods of elevated protein excretion are relatively limited in minimal-change disease and may be inadequate to generate injury (41). Patients with this disease who have only a few relapses are protected from progressive renal damage (42), whereas those who initially responded to glucocorticoid therapy but then have frequent relapses tend to develop focal glomerulosclerosis (43–46). In patients with permanent proteinuria and nephrotic syndrome caused by minimal-change disease that is resistant to treatment,

Figure 1. **Effect of increased glomerular permeability to proteins on progressive renal injury.**


Renal injury
Nephron mass reduction
Glomerular capillary hypertension
Increased glomerular permeability to macromolecules
Increased filtration of plasma proteins
Proteinuria
Albumin
Transferrin
IgG
Complement factors
TGF-β
IGF-I
Angiotensin II
Excessive tubular reabsorption of proteins
Nuclear signals for NF-κB–dependent genes
Release of vasoactive and inflammatory substances into the interstitium
Increased TGF-β synthesis
Transdifferentiation of tubular cells to myofibroblasts
Inflammatory cell recruitment into the interstitium
Tubular-cell hypertrophy
Cytokine and growth factor release
Increased type IV collagen
Fibroblast proliferation
Fibrogenesis
Renal scarring

renal function inevitably deteriorates with time (47). The few patients who have undergone repeated renal biopsies show interstitial inflammation and fibrosis, with an increasing number of sclerotic glomeruli over time (48).

Primary tubulointerstitial nephritis also appears to be indolent with regard to progression to end-stage renal disease, despite the hypothetical relationship between the degree of interstitial damage and the rate of renal function decline (49). This may occur because during the early stages of interstitial nephritis, tubular functional abnormalities are more pronounced than is the decline in glomerular filtration rate (GFR). At the time of the initial insult, injury is limited to segmental loci of the tubulointerstitial areas, with almost all glomeruli structurally and functionally intact; thus, renal functional reserve is completely preserved (50). Glomerular abnormalities arise only in advanced stages of primary tubulointerstitial nephritis; they are a consequence of adaptive alterations to glomeruli or of the injurious effects of tubulointerstitial processes. In such circumstances, excess protein leakage from glomeruli into the tubular lumen and the resulting reabsorption of excess proteins by proximal tubular cells may have additional interstitial damaging effects, which accelerate the progression of renal disease.

The pivotal role of enhanced protein traffic as a predictor of end-stage renal disease and its impact on renal outcome are clearly illustrated by the Ramipril Efficacy in Nephropathy (REIN) study. This study formally investigated whether excessive ultrafiltration of proteins influenced the progression of renal disease and whether an ACE inhibitor (ramipril) was superior to placebo and other antihypertensive drugs in reducing proteinuria, limiting the decline in GFR, and preventing end-stage renal disease in patients with and without hypertension; blood pressure was controlled at similar levels in both treatment groups (51). The REIN study is a randomized, double-blind, placebo-controlled, multicenter clinical trial in 352 nondiabetic patients with clinical proteinuria (≥ 1 g/24 hours). Patients were randomly assigned to receive ramipril or conventional antihypertensive therapy to maintain diastolic blood pressure at 90 mm Hg or less. A prestratification strategy recognized two levels of proteinuria (stratum 1: >1 and <3 g/24 hours; stratum 2: ≥ 3 g/24 hours) in patients randomly assigned to ramipril or conventional antihypertensive therapy.

In this trial, the only baseline variable that correlated significantly with decline in GFR and progression of disease to end-stage renal failure was urinary protein excretion. Thus, patients with baseline urinary protein excretion less than 2.5 g/24 hours had a low rate of GFR decline over 3 years of follow-up, whereas in those with proteinuria in the nephrotic range (>4.3 g/24 hours), GFR decreased by 10 mL/min per 1.73 m^2 of body surface area per year and the kidney failure rate exceeded 50% at 3 years (52).

THE RENOPROTECTIVE EFFECT OF RENIN–ANGIOTENSIN SYSTEM INHIBITION: THE REIN STUDY

The REIN study showed that despite similar blood pressure control in the two treatment groups, patients with proteinuria of 3 g/24 hours or more who received the ACE inhibitor had a significantly lower rate of decline in GFR and lower risk for doubling of serum creatinine levels or end-stage renal failure than did patients receiving conventional antihypertensive therapy (51). On the other hand, the authors found that the ramipril-induced reduction in rate of urinary protein excretion was the only time-dependent covariate that predicted a lower decline in GFR and lower incidence of progression to end-stage renal disease; this finding clearly indicated that renoprotection is linked to reduction of protein traffic (51).

On the basis of interim data analysis, the core study of the REIN trial was stopped by an independent adju-

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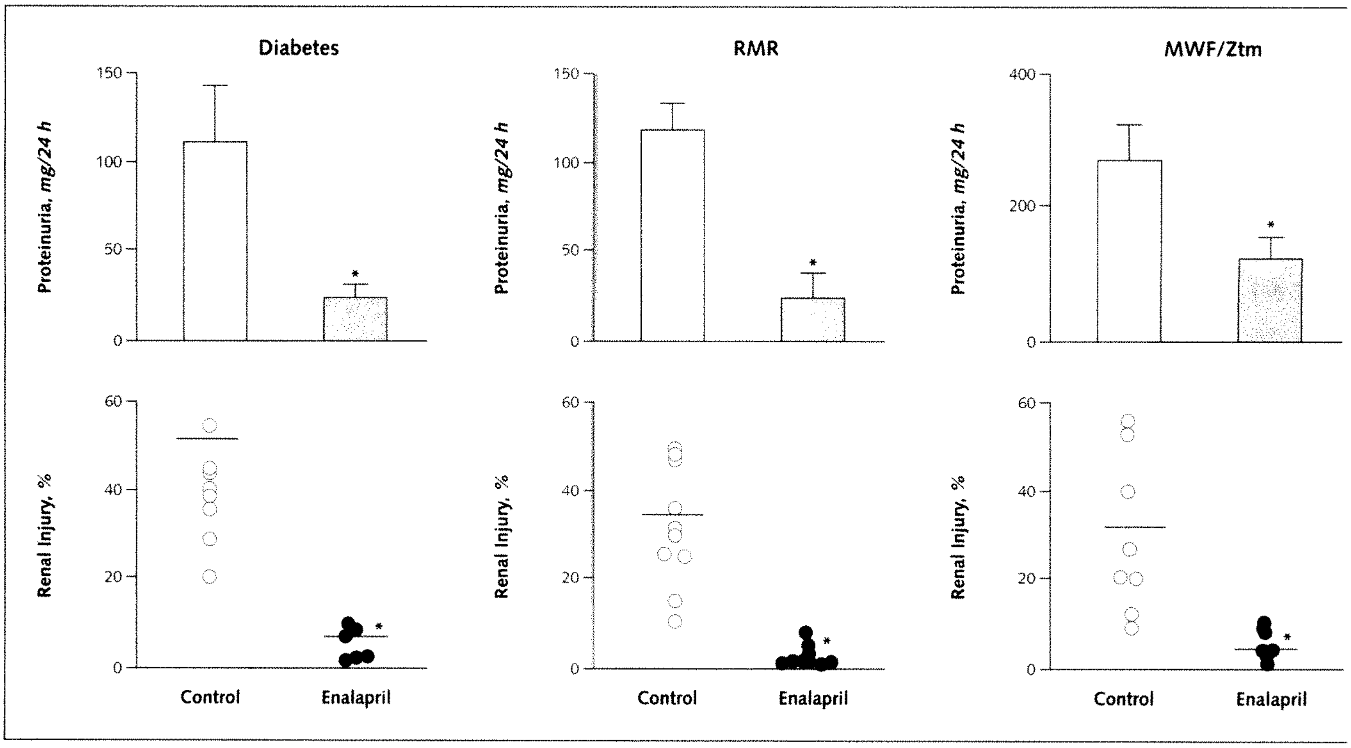
Compensatory glomerular hemodynamic changes in response to nephron loss caused by the original renal insult lead to increased intraglomerular capillary pressure, which impairs the size-selective function of the glomerular permeability barrier and causes protein ultrafiltration. Excessive reabsorption of proteins as a consequence of the increased glomerular permeability results in protein accumulation in proximal tubular cells. Congestion of endolysosomes and endoplasmic reticulum in proximal tubular cells may trigger the activation of genes encoding vasoactive and inflammatory mediators (endothelin, RANTES [regulated upon activation, normal T-cell expressed and secreted], monocyte chemoattractant protein-1, and other cytokines). In addition, enhanced generation of transforming growth factor-β (*TGF-β*) causes tubular cell hypertrophy and collagen type IV production. Tubular cells may also become activated to transdifferentiate into myofibroblasts. Release of excessive vasoactive and inflammatory substances from the proximal tubular cells into the interstitium contributes to interstitial inflammation and fibroblast proliferation, eventually inducing increased synthesis of extracellular matrix and renal scarring. IGF-I = insulin-like growth factor-I; NF-κB = nuclear factor-κB.

dicating panel; the panel recommended that all patients in stratum 2 be given the most effective treatment. Thus, patients who were receiving ramipril at the start of the study, as well as those originally randomly assigned to conventional therapy and then switched to ramipril, were formally followed for another 2 years (the REIN follow-up study) (53). In patients continuing to receive ramipril, GFR further decreased by approximately 1 mL/min per year during follow-up (**Figure 3**). The decrease was similar to that associated with normal aging. This finding is reminiscent of early results in patients with diabetic nephropathy. Antihypertensive therapy continued for a long enough period was associated with a progressive reduction in GFR decline; GFR decline was only 1.2 mL/min per year after 6 years of treatment (54). Patients who switched from conventional therapy to ramipril also benefited from the treatment, as shown by a greater reduction in GFR during follow-up than during the core study (**Figure 3**).

Results of an analysis of outcome events were consistent with the GFR data. Considering both the core and follow-up phases of the REIN study, patients originally randomly assigned to ramipril had a significantly lower incidence of progression to end-stage renal disease (51, 53). Perhaps most impressive is the finding that after about 36 months of treatment with ramipril, no additional patients progressed to the point of requiring dialysis, whereas patients switched from conventional therapy to ramipril continued to develop end-stage renal disease. During the core study, ramipril was associated with a 41.5% reduction in the risk for end-stage renal disease, whereas during the follow-up phase, patients initially randomly assigned to ramipril had a 66.1% reduction in the risk for reaching this end point.

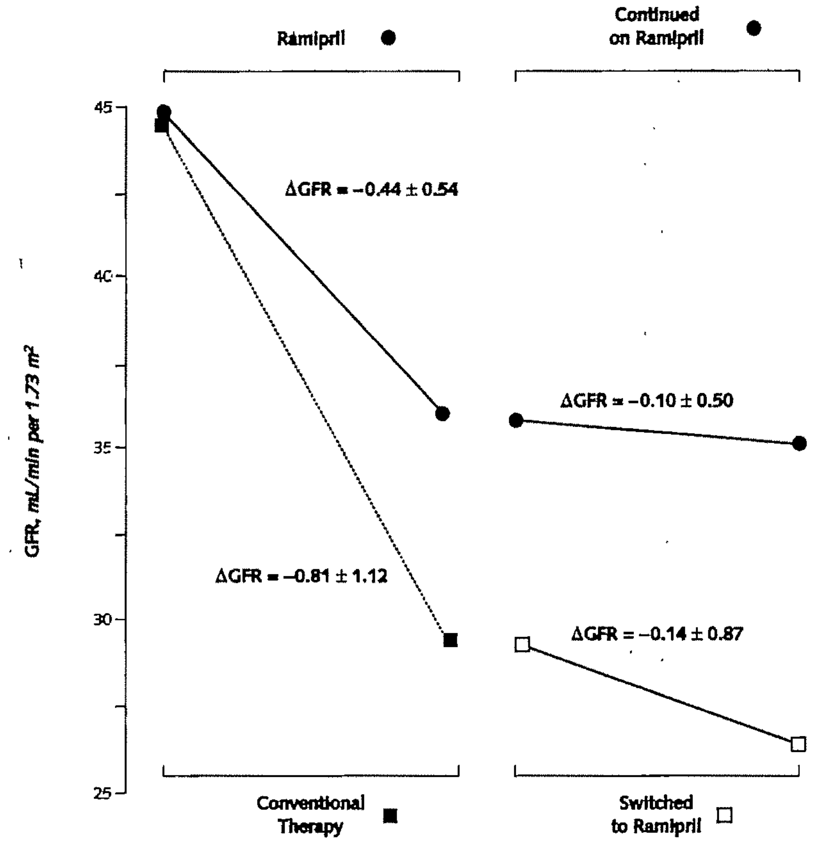
How can we explain the continued improvement in patients who continued to receive ramipril? In patients who initially received ramipril, a small increase in GFR over the first 3 months was followed by a slow decline. After 30 to 36 months of treatment, however, GFR did not decrease further, and, from 36 to 48 months, the

Figure 2. **Limiting protein traffic prevents progression of renal disease in animals.**



In experimental diabetes among rats with a remnant kidney and male Munich Wistar Fromter/Ztm (*MWF/Ztm*) rats (all animal models in which progressive proteinuria and renal injury develop with time), inhibition of angiotensin-converting enzyme with enalapril consistently exerts antiproteinuric and renoprotective properties. $^*P < 0.01$ versus control. In the top panel, white bars represent control rats and gray bars represent rats receiving enalapril. In the bottom three panels, each circle represents an individual rat. Diabetes = streptozotocin-induced diabetes; RMR = renal mass reduction.

Figure 3. **Mean decline in glomerular filtration rate (*GFR*) during the Ramipril Efficacy in Nephropathy (REIN) core and follow-up study in patients with nondiabetic chronic proteinuric nephropathies.**



Treatment	Events, *n* Core Study	Events, *n* Follow-up
Ramipril–Ramipril	18	6
Conventional–Ramipril	40	14

Solid lines indicate ramipril therapy and the dotted line indicates conventional therapy. Black circles indicate continued ramipril therapy during the core and follow-up study; black and white squares indicate a switch in treatment from conventional therapy (during the core study) to ramipril (during the follow-up study). The decline in GFR (in mL/min per 1.73 m^2 per month) was significantly lower during the follow-up study than during the core study in the patients originally randomly assigned to ramipril or to placebo plus conventional antihypertensive therapy. The GFR was better preserved and the number of renal outcome events (for example, end-stage renal failure) was lower in patients receiving ramipril during the core and follow-up studies than in those who originally received conventional antihypertensive therapy and switched to ramipril in the follow-up phase.

mean GFR actually increased, suggesting that patients may have reached a stage of disease regression (55). This remarkable outcome should be considered in light of the fact that all these patients had proteinuria greater than 3 g/24 hours before the study and therefore would have been expected to have a rapid decline in GFR. Thus, after 60 months of ramipril treatment, the rate of renal function decline was less than one tenth of the decline seen in patients receiving conventional therapy during the core study (0.9 mL/min per month) (55).

We must concede, however, that these findings may have been affected by a selection bias resulting from different periods of follow-up. We have formally analyzed this issue and found that in all the cohorts of patients with different periods of follow-up, the GFR decline was slower in patients who continued to receive ramipril therapy than in those who switched to ramipril during follow-up (55). More important, in each cohort of patients receiving continued ramipril therapy, renal function tended to improve progressively as the follow-up period (18 to 60 months) increased.

To further investigate the nature of the time-dependent improvement in GFR change, we looked for a breakpoint in the individual GFR slopes of patients receiving continued ramipril therapy. We predicted that after the breakpoint, 10 patients receiving continued ramipril therapy would never progress to end-stage renal disease and that another 10 had such improved GFR slopes that progression to end-stage renal disease would be delayed by about 5 years (55).

This analysis provides evidence that the tendency of GFR to decline with time can be halted in some patients with chronic nephropathies. The clinical relevance of these findings rests on the fact that patients recruited in the REIN study were selected for severe disease, which resulted in a study sample expected to rapidly progress to end-stage renal disease if left untreated. These findings agree with previous findings in proteinuric Munich Wistar Fromter rats (a genetic model of progressive nephropathy) that late-onset ACE inhibition normalized blood pressure and gradually reduced the high protein excretion rate toward normal values, arresting the progression of tissue damage (56). The same is true for remission of the nephrotic syndrome in diabetic patients receiving long-term ACE inhibitor treatment (57). Thus, both experimental and clinical data strongly suggest that remission is now achievable in some patients with chronic renal disease.

A STEPWISE MULTIMODAL PROTOCOL FOR MANAGING RENAL DISEASE PROGRESSION

Because of the current lag time between start of treatment and remission, a substantial proportion of patients still progress to end-stage renal disease before their renal function begins to stabilize. The goal should be to investigate strategies for limiting the number of patients progressing to end-stage renal disease during the initial treatment periods. Ad hoc studies should explore whether this can be achieved by starting therapy very early in patients with chronic renal disease, when GFR is greater than 60 mL/min. Transplantation of a single kidney merits special attention because a single kidney theoretically supplies half the number of nephrons usually available to healthy patients. This implies an increased workload per nephron to maintain homeostasis. In the transplanted kidney, the pool of functioning nephrons is also likely to decrease as a result of the initial ischemic injury, acute rejection, and long-term drug toxicity. Thus, self-perpetuating adaptive hemodynamic changes occur (as in progressive proteinuric nephropathies); these changes may ultimately contribute to renal function deterioration and scarring (58, 59).

The potential renoprotective effect of renin–angiotensin system blockade in clinical transplantation has been seen only in studies with short-term follow-up; these studies show that these agents can reduce urinary protein excretion. However, it is too soon to predict the long-term impact of these drugs on kidney graft survival.

When early treatment is not feasible because of late referral to nephrologists, the current therapeutic approach, based on ACE inhibitors, can be optimized by adding other agents to reduce the risk for progression to end-stage renal disease. The first step in this multimodal approach relies on a low-sodium diet in addition to pharmacologic blockade of the renin–angiotensin system with ACE inhibitors. Low but not high sodium intake activates the intrarenal renin–angiotensin system, which potentiates the efficacy of ACE inhibitors. In patients with chronic nephropathies, treatment with lisinopril and a low-salt diet (3 g/d) provided a higher antiproteinuric effect than did the same ACE inhibitor with a high-salt diet (12 g/d) (60). Moreover, the blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored with diuretics, as was recently documented in patients receiving an ACE inhibitor and hydrochlorothiazide in addition to a high-sodium diet (61).

If progression of renal disease is still not satisfactorily controlled, an attempt should be made to maximize the antiproteinuric effect of the currently used ACE inhibitor. One possibility is to increase the drug dose to a level higher than the recommended threshold. The rationale for this suggestion rests on experimental data from rats with subtotal nephrectomy. In that study, the ACE inhibitor was given in dosages exceeding the required antihypertensive dose; this resulted in additional benefit to the glomerular structure (that is, reversing early glomerulosclerosis) compared with a low antihypertensive dose (62).

We evaluated the effects of different dosages of ramipril, from a minimum of 5 mg/d to a maximum of 20 mg/d (four times the recommended maximum dosage) on the level of proteinuria. Although the higher dosages had no additional effect on blood pressure, urinary protein excretion rates were further reduced, suggesting that the use of blood pressure alone to titrate the dosage may not achieve the maximum renoprotective effect (63). Similarly, doses of angiotensin II receptor antagonist higher than the maximum recommended doses further reduced urinary protein excretion, without causing significant changes in blood pressure or serum creatinine and potassium levels (64). Because of the preliminary nature of these data, caution should be used in adopting this regimen, and blood pressure control as well as potential side effects must be closely monitored.

An alternative is the multidrug approach that combines ACE inhibitors and angiotensin II receptor antagonists. The advent of angiotensin II receptor blockers extended the therapeutic options to slow the progression of chronic renal disease because these drugs inhibit the renin–angiotensin system at different levels than do ACE inhibitors; thus, they may act synergistically. Data on the use of combinations of an ACE inhibitor and an angiotensin II receptor antagonist in humans are extremely limited. Preliminary studies in sodium-depleted persons with normal blood pressure and in diabetic patients with normal renal function found a greater reduction in blood pressure after the addition of losartan to enalapril treatment than after doubling of the enalapril dose; this suggests that the combination more effectively inhibited the renin–angiotensin system (65).

In a pilot study of 11 patients with chronic renal disease of various causes, the investigators reported that 2 weeks after the addition of an angiotensin II receptor antagonist to ACE inhibitor therapy, there were an additional 30% reduction in proteinuria, a 6-mm Hg decrease in mean arterial pressure, and no changes in creatinine clearance (66). Proteinuria and blood pressure were significantly lower in patients with type 2 diabetes and overt nephropathy when an angiotensin II receptor antagonist was added to the initial treatment regimen with maximum recommended doses of an ACE inhibitor (67). An additive antiproteinuric effect of ACE inhibition and angiotensin II receptor antagonism has been reported in normotensive patients with IgA nephropathy; systemic blood pressure was not affected (68).

Taken together, these preliminary studies suggest that adding an angiotensin receptor antagonist may help maximize the antiproteinuric effect of ACE inhibitors. Prospective trials will reveal whether combined therapy is actually more renoprotective than single therapy.

A potential side effect of these treatments is hyperkalemia, especially in patients with renal failure and those with diabetes. However, in a pooled analysis of six published trials that included 154 diabetic and nondiabetic patients with chronic proteinuric nephropathies (51, 53, 69–72), the incidence of dropout due to uncontrolled hyperkalemia was similar: less than 2% in the renin–angiotensin system blockade and conventional treatment groups. The risk for hyperkalemia can be minimized by excluding patients with renovascular disease. In patients being treated with drugs that inhibit the renin–angiotensin system, serum potassium levels should be closely monitored, hyperglycemia and metabolic acidosis should be promptly treated, and thiazide or loop diuretics should be recommended.

Calcium-channel blockers are often used in patients with renal disease. Whether these drugs add benefit to the renoprotective properties of ACE inhibitors is controversial. Nondihydropyridine calcium-channel blockers reduced proteinuria in humans with type 2 diabetes and overt nephropathy (73) and, combined with ACE inhibitors, produced a greater reduction in proteinuria than did higher doses of either agent alone; similar levels of blood pressure control were maintained. Despite the lack of controlled studies, these observations suggest that combined treatment with nondihydropyridine calcium-channel blockers and ACE inhibitors may be more renoprotective than either treatment alone.

Data on dihydropyridine calcium-channel blockers are less encouraging because they indicate that these agents may worsen the progression of chronic nephropathies. In the REIN study, patients receiving dihydropyridine calcium-channel blockers had a higher level of proteinuria and faster decline in GFR than patients treated with other antihypertensive drugs; in both groups, blood pressure control and severity of underlying renal disease were similar (74). The excess proteinuria was greater for patients with poor blood pressure control or without concomitant ACE inhibition. These findings, combined with the evidence that these drugs may increase cardiovascular risk (75), particularly in patients with diabetes with or without renal disease, suggest that dihydropyridine calcium-channel blockers should not be given to patients with chronic nephropathies of nondiabetic or diabetic origin. An exception is when ACE inhibitors, diuretics, and β-blockers fail to reduce blood pressure to the appropriate level.

THE NEED TO CONTROL BLOOD PRESSURE AND THE LIPID PROFILE

The proposed strategies to reduce proteinuria should be combined with other pharmacologic interventions aimed at controlling blood pressure and the lipid profile, as well as modifying the diet and habits of patients with chronic renal disease.

Hypertension, the hallmark of most chronic nephropathies, is a strong independent risk factor for end-stage renal disease (38, 76); reducing blood pressure consistently slows the progression of renal disease and reduces injury (77). A meta-analysis found a strong relationship between the extent of blood pressure control and reduction in proteinuria in patients who have type 1 and type 2 diabetes with microalbuminuria and macroalbuminuria (78). Whenever blood pressure was well controlled, all antihypertensive drugs except the dihydropyridine calcium-channel blocker nifedipine significantly reduced proteinuria. Thus, close monitoring of blood pressure is essential in slowing the progression of both diabetic and nondiabetic renal disease.

Dyslipoproteinemia is seen with chronic renal insufficiency from the early stages of renal functional impairment (79); it accelerates atherosclerosis and progression of the renal disease (80). A meta-analysis of 13 prospective controlled trials supports the possibility of a causal relationship between dyslipidemia and disease progression; the analysis found that lipid reduction may reduce proteinuria and preserve GFR in patients with chronic renal disease (81).

A few initial studies showed a low-protein diet to be beneficial, but larger trials were less encouraging. A meta-analysis of 13 randomized trials (1919 patients) and 11 nonrandomized, controlled trials (2248 patients) indicate that protein restriction had significantly more effect in the nonrandomized trials (82). In the randomized trials, low protein intake was associated with only a mild (not significant) reduction in the decline in GFR. Thus, the benefit of a low-protein diet in slowing the progression of renal failure is negligible or, at best, small. The poor nutritional status often seen in patients adherent to the diet must also be considered.

Finally, impressive findings indicate the importance of smoking cessation. This is perhaps the single most important measure to protect kidneys from progressive disease (83–85). Unfortunately, patients and their physicians do not tend to appreciate the importance of smoking cessation.

CONCLUSIONS

We now have compelling clinical evidence of the renoprotective effects of ACE inhibitors in patients with nondiabetic chronic renal disease. In hypertensive patients with chronic renal failure, ACE inhibition slows progression toward end-stage renal disease more than β-blockers do, through a mechanism at least partially independent of blood pressure control (71). Therapy with ACE inhibitors also improves long-term dialysis-free survival in patients with progressive chronic renal failure, an outcome influenced by the magnitude of protein excretion rate and the initial antiproteinuric response to therapy (70).

A meta-analysis of 10 randomized trials confirmed that ACE inhibitors are more effective than other antihypertensive agents in slowing the progression to end-stage renal disease in nondiabetic patients, although it was not clear whether this benefit was due to the greater decline in blood pressure or to other effects (86). The REIN core study showed that at similar levels of blood pressure control, ACE inhibitors are more effective than conventional antihypertensive therapy in reducing proteinuria, slowing GFR decline, and limiting progression to end-stage renal disease. Finally, in the follow-up phase of the REIN study, prolonged (>36 months) ACE inhibitor therapy helped arrest the decline in GFR (disease remission). In a small number of patients with the longest follow-up, there was even a small increase in GFR with time, possibly signifying regression of the disease.

In the future, we should be able to reduce the time required to induce remission by optimizing renoprotection with multimodal interventions (87) achieved by combining antihypertensive medications, lowering lipids, and stopping smoking; in addition, for patients with diabetes, tight blood glucose control is critical. Several new compounds are under evaluation in animal studies, and it is hoped that they will soon become part of the treatment strategy.

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Balancing Safety of Dietary Supplements with the Free Market

A desire to take medications is, perhaps, the greatest feature which distinguishes man from other animals.

–Sir William Osler, 1891

In this issue, Favreau and colleagues report on cases of hepatotoxicity in users of the dietary supplement Lipo-Kinetix (1). This dietary supplement was marketed as a weight-loss product and contained norephedrine (also known as phenylpropanolamine), caffeine, yohimbine, diiodothyronine, and sodium usniate. The authors report the experience of seven patients, each taking Lipo-Kinetix for weight loss, who experienced severe liver injury within 12 weeks of ingesting this product.

This and other recent reports of adverse outcomes associated with use of supplements (2, 3) highlight two important issues that merit further consideration: 1) regulation and safety of dietary supplements and 2) safety surveillance.

The U.S. Congress has distinguished between what the U.S. Food and Drug Administration (FDA) considers to be a drug and a dietary or nutritional supplement. This regulatory distinction, however, is not based on biological data. Rather, it is a question of labeling. A product is considered to be a drug when it claims that it can treat, prevent, cure, mitigate, or diagnose a specific disease (4). In contrast, supplements can make only "structure/function" claims, such as "maintains a healthy circulatory system" (5).

To understand this distinction, one must consider the history of drug and supplement labeling. In 1937, 107 people in the United States died after exposure to elixir sulfanilamide as a result of the diethylene glycol solvent used in the elixir (6). In response to this event, Congress enacted the Food, Drug and Cosmetic Act of 1938, which required proof that a drug was safe before it could be marketed. Several decades later, the epidemic of birth defects associated with thalidomide use led to the 1962 Kefauver–Harris Amendment to the Food, Drug and Cosmetic Act (6). For the first time, manufacturers were required to report all adverse events to the FDA. In addition, with this legislation, proof of efficacy was required for FDA approval (6).

Proof of efficacy is established in randomized trials, often requiring only a few tens or hundreds of patients. Safety, however, can be much more difficult to prove and generally requires that between 500 and 3000 patients be exposed to a new drug during premarketing studies (7). Despite this, rare and late risks associated with long-term use of new compounds are not known at the time of marketing. Major changes in labeling are made for fully 51% of drugs because of safety problems found after the drugs are marketed (8).

In contrast to the requirements for approval of a new drug, dietary supplements are held to a much lower standard. The 1990 Nutrition Labeling and Education Act (NLEA) limited health claims for food and supplement labeling to seven categories: 1) calcium and osteoporosis, 2) sodium and hypertension, 3) saturated fat and cholesterol and heart disease, 4) dietary fat and cancer, 5) fiber-containing grain products, fruits, and vegetables and cancer, 6) fruits and vegetables and cancer, and 7) fiber-containing grain products, fruits, and vegetables and heart disease (9). Some people believed that the NLEA limited the development of dietary supplements, despite public demand for these products (9, 10). The combined perception of safety, public desire for increased access, and industry desires for easy access to the market made this an easy target for legislators. The Dietary Supplement Act of 1992 exempted supplements from the NLEA (9). The Dietary Supplement Health and Education Act (DSHEA) of 1994 gave the public even greater access to dietary supplements so that consumers could be further empowered to actively participate in improving their own health (9, 10).

According to the DSHEA, a dietary supplement was defined as

> a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing total daily intake, or a concentrate, metabolite, constituent, extract or combination of these ingredients (11).

In addition, a 2001 FDA overview of dietary supplements states:

> Under DSHEA, a firm is responsible for determining that the dietary supplements it manufactures or distributes are safe and that any representations or claims

> made about them are substantiated by adequate evidence to show that they are not false or misleading. This means that dietary supplements do not need approval from FDA before they are marketed. Except in the case of a new dietary ingredient, where pre-market review for safety data and other information is required by law, a firm does not have to provide FDA with the evidence it relies on to substantiate safety or effectiveness before or after it markets its products (12).

Even for new ingredients, the manufacturer is only required to provide evidence to the FDA that the product is "reasonably expected to be safe" (12).

The postmarketing reporting requirements for manufacturers of drugs and dietary supplements also differ substantially. Manufacturers of drugs must provide information to the FDA when they learn of any adverse event potentially related to their drug. Most data on adverse drug events are collected via direct contact between health care providers or patients and manufacturers or via the FDA's spontaneous reporting system MedWatch (6). In contrast, manufacturers of supplements are not required to report any data on adverse events to the FDA, and the FDA must prove that the product is unsafe before it can restrict a product's use (12).

How then is the FDA to identify unsafe dietary supplements? The FDA largely relies on the MedWatch spontaneous reporting system to collect safety data on dietary supplements. On the basis of the adverse event reports submitted via MedWatch, on 19 November 2001, the FDA strongly recommended to the manufacturer that Lipo-Kinetix be removed from the market (13).

Although this notification from the FDA may be viewed as a great success of MedWatch, several features of this system severely limit its ability to deal with dietary supplements (6). The MedWatch system relies on "voluntary" reporting of suspected adverse drug reactions. Thus, the patient or health care provider must actually recognize the event as a possible adverse drug reaction. A recent survey demonstrated that only 16% of internal medicine clerkships had formal lectures on adverse drug reactions (14). It is possible that many, if not most, adverse reactions may go unrecognized by the patient or health care provider as being medication related. Even if adverse drug reactions are recognized, reporting rates are extremely low. Probably fewer than 10% of all adverse drug reactions and an even lower proportion of less serious events are reported (6). For dietary supplements, the rates are probably even lower. Finally, even when the FDA receives spontaneous reports, interpretation is difficult. In essence, spontaneous reports represent case reports or case series. When enough reports are received, a signal of a possible problem may emerge, but proving causality from case reports and case series is very difficult. Incidence rates are almost impossible to estimate from spontaneous reporting systems, and there is no control group against which to compare the spontaneous reports. When proof of a signal is required, formal pharmacoepidemiology studies may be needed (7).

Reporting by physicians to the MedWatch system is crucial. It is the best available method to discover potentially harmful medications and dietary supplements. Recently, several medications and dietary supplements have been withdrawn from the market as a result of spontaneous reporting. These actions may have saved many lives. Until a better system is available, it is the health care community's responsibility to work with the FDA to ensure the safety of our medications and dietary supplements. A need remains, however, for the health care system and government agencies to reconsider how both drugs and dietary supplements are monitored. Clearly, additional postmarketing safety systems are required.

Although better postmarketing safety systems would help, perhaps a more important question is whether the time has come to reconsider the requirements for marketing dietary supplements. We require proof that prescription drugs are sufficiently safe and effective before marketing. We require proof that over-the-counter drugs are extremely well studied, effective, and very safe before we permit them on the market for consumer use. Yet, there are no data for most supplements, merely because they do not claim to prevent or treat specific medical conditions. For supplements, there are no regulations to ensure appropriate dose recommendations, proof of efficacy, or appropriate investigation into potential toxicities or interactions with other supplements or medications. Even quality control is not assured, that is, that the product includes what is stated on the label (15, 16). In essence, supplements exist in a "data-free world." In the United States, the public spends almost $4 billion yearly on supplements (15), with little or no data on what they can expect. We rely on the market to prove efficacy and safety, a strategy that failed before with prescribed drugs and resulted in the establishment of the FDA. We should learn from our experiences. Perhaps the time has come to hold the manufacturers of any product with a health claim to the same standards as the pharmaceutical industry.

A complete description of a system to regulate nutritional supplements is beyond the scope of this editorial, but it is easy to imagine some basic features that might be incorporated into the system. Regulations should require that any health claims be supported by data approved by the FDA. For example, health claims, such as improving cardiovascular health, should meet the same rigorous criteria as claims to prevent or treat a disease. Another key to a new system would be to set and enforce standards to document the content of products. Unfortunately, the active component of most nutritional supplements is unknown, thus creating an additional challenge to regulate production (17). Finally, new legislation should mandate that any adverse event reported to a manufacturer must be forwarded to the FDA. This would improve the ability to identify and remove unsafe products in a more timely fashion.

Until such change can be enacted, it is our responsibility to keep the FDA aware of any suspected toxicities related to drugs and supplements so that the currently available safety net can work as well as possible. Suspected adverse events from medications should be promptly reported to the FDA through the MedWatch system at their Web site (www.fda.gov/medwatch), telephone (800-FDA-1088), or fax (800-FDA-0178).

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CLINICAL GUIDELINE

The Role of High-Dose Chemotherapy and Stem-Cell Transplantation in Patients with Multiple Myeloma: A Practice Guideline of the Cancer Care Ontario Practice Guidelines Initiative

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The Hematology Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative has systematically reviewed the published literature and, through a consensus process, developed an evidence-based practice guideline assessing the role of stem-cell transplantation in patients with multiple myeloma. The conclusions were validated by solicited feedback from 221 practitioners across Ontario, Canada. The guideline comprises six recommendations: 1) Autologous transplantation is recommended for patients with stage II or III myeloma and good performance status. Evidence of benefit is strongest for patients who are younger than 55 years of age and have a serum creatinine level less than 150 μmol/L (<1.7 mg/dL). Physicians must use clinical judgment in recommending transplantation to other patients. 2) Allogeneic transplantation is not recommended as routine therapy. 3) Patients potentially eligible for transplantation should be referred for assessment early after diagnosis and should not be extensively exposed to alkylating agents before collection of stem cells. 4) Autologous peripheral blood stem cells should be harvested early in the patient's treatment course. The best available data suggest that transplantation is most advantageous when performed as part of initial therapy. 5) The comparative data addressing the specifics of the transplantation process are insufficient to allow definitive recommendations. In the absence of such data, a single transplant with high-dose melphalan, with or without total-body irradiation, is suggested for patients undergoing transplantation outside a clinical trial. 6) At this time, no conclusions can be reached about the role of interferon therapy after transplantation.

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After more than three decades of clinical trials testing various standard-dose chemotherapy regimens, the disease course of patients with multiple myeloma has not changed appreciably. Conventional chemotherapy can provide effective palliation but is not curative (1). Case series have described encouraging results in patients with myeloma undergoing allogeneic or autologous bone marrow or peripheral blood stem-cell transplantation (2). Other studies of transplantation, including randomized trials, have been reported in the past 6 years (3, 4).

To facilitate decisions about treatment options, practice guidelines have been developed for use by health care providers and consumers. In Ontario, Canada, cancer treatments and policies are led by a state-funded organization, Cancer Care Ontario. To help derive treatment options, Cancer Care Ontario has developed the Program in Evidence-Based Care, which includes the Practice Guidelines Initiative. Disease Site Groups (DSGs), which comprise physicians, epidemiologists, and consumers, develop guidelines through a systematic process that involves assessment of evidence, consensus, and a validation process involving practitioners from across the province. Guideline topics are chosen through a prioritization process that includes the burden of illness, availability of evidence, perceived variation in practice, the potential to affect treatment decisions, and resource utilization.

The Hematology DSG noted that the use of transplantation for patients with myeloma varied among practices across the province. Variability in practice and emerging evidence of higher quality made this a priority topic for guideline development. To approach this topic, the DSG addressed the following questions: What is optimal standard-dose chemotherapy for patients with myeloma? In terms of survival, is peripheral blood stem-cell or marrow transplantation better than conventional chemotherapy? What is the relative efficacy of autologous versus allogeneic transplantation? What specifics of the transplantation process can be recommended? When should transplantation be performed? Who should (or should not) receive a transplant?

METHODS

Overview of Guideline Development

This guideline was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) using

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the methods of the Practice Guidelines Development Cycle (5). Members of the CCOPGI's Hematology DSG selected, reviewed, and interpreted the evidence. This DSG comprises 25 members, including hematologists, medical and radiation oncologists, an epidemiologist, and 2 lay representatives. Several of the physician members have background training in epidemiology; 8 hematologists regularly perform stem-cell transplantation in clinical practice.

The DSG's draft recommendations were circulated through a mailed survey to hematologists and medical or radiation oncologists in Ontario for feedback and involvement in a consensus process. Responses were used to guide the reformatting of the draft into the final guideline recommendations. The Practice Guidelines Co-ordinating Committee (PGCC), which ensures consistency of guideline development across the DSGs of various tumor sites, approved the guideline. The CCOPGI has a standardized process to update each guideline report; the current guideline was updated and reviewed by the PGCC in October 2000.

Literature Search Strategy

We searched the MEDLINE, CANCERLIT, and Cochrane Library databases for literature published from 1992 to December 1997 and subsequently updated the search in October 1998, June 1999, and April 2000. For the searches, we combined *multiple myeloma* (as a Medical Subject Heading [MeSH] and text word) with *bone marrow transplantation* (MeSH and text word) and *drug therapy* (MeSH). Then, we combined these terms with the search terms for the following study designs: *practice guidelines*; *systematic reviews* or *meta-analyses*; *reviews*; *randomized controlled trials*; *controlled clinical trials*; and *comparative studies*. In addition, we searched the PubMed and Physician Data Query (PDQ) (www.cancer.gov/search/clinical_trials/) databases and reviewed relevant conference proceedings (American Society of Hematology, 1997 to 1999, and American Society of Clinical Oncology, 1999 to 2000), article bibliographies, and personal files. To address the issue of optimal chemotherapy, we performed an additional search of the same databases using the term *multiple myeloma* (MeSH) combined with *randomized controlled trials* (MeSH) and the text word *random* in the title.

Inclusion Criteria

We selected study reports meeting one of the three following criteria: randomized trial or meta-analysis of therapy for patients with myeloma that reported survival or quality-of-life outcomes; nonrandomized comparative trial that addressed transplantation strategy, including a contemporaneous control group, and that reported survival or quality-of-life outcomes; or economic evaluation that addressed transplantation strategy. Because of insufficient data on the specifics of the transplantation process and the patients who would be most likely to benefit from transplantation, we performed a second search, which identified data from noncomparative case-series studies.

Data Extraction and Interpretative Summary

Three members of the DSG, including an epidemiologist, determined eligibility of the articles and abstracts obtained from the literature search. The lead DSG member for this guideline extracted and summarized relevant data according to the guideline question addressed. The DSG members then reviewed the summarized data and key articles. The DSG met formally three to four times annually; at these meetings, the members methodologically assessed the articles, interpreted the data, and debated specific points in an attempt to reach a consensus.

Synthesizing the Evidence

Because all of the nine randomized trials on transplantation addressed different questions, we did not statistically pool the data.

DSG Consensus Process

Through an iterative process that included debate at formal meetings and circulation of draft recommendations, we considered the implications of the appraised data for each guideline question. With this process, attempts were made to reach consensus; when this was impossible, minority opinions were recorded. Approval by each member of the DSG was required before circulation of the draft version for practitioner feedback and submission of the final guideline to the PGCC.

Practitioner Feedback

To obtain practitioner feedback, we mailed a survey to 211 practitioners in Ontario (94 hematologists, 93 medical oncologists, and 24 radiation oncologists). The survey consisted of standardized items asking the practitioner to rate the quality of each draft guideline and to judge whether the draft recommendations should serve as a practice guideline. Written comments were invited. Follow-up reminders were sent at 2 weeks (by postcard) and 4 weeks (entire package). After exclusion of 18 retired practitioners, 137 of 193 practitioners (71%) responded; 90 of 137 respondents (66%) indicated that the guideline was relevant to their practice. Approval of the draft guideline was strong among these 90 practitioners: 91% agreed or strongly agreed that the summary of the evidence was acceptable, 87% agreed with the draft recommendations, and 81% approved of the recommendations as a practice guideline. Thirty-nine respondents provided written comments; these comments were, like the other responses, incorporated in the final guideline.

RESULTS

Sixty-six reports met the criteria for inclusion and are categorized in Table 1. In each section below, we describe the studies, summarize results, and describe the guideline development.

What Is Optimal Standard-Dose Chemotherapy for Patients with Multiple Myeloma?

To properly compare transplantation with conventional chemotherapy, we must define optimal conventional chemotherapy. We identified 30 randomized trials comparing therapies in previously untreated patients. Four meta-analyses (6–9) evaluated these data.

The Myeloma Trialists' Collaborative Group (7) compared combination chemotherapy with melphalan plus prednisone in a meta-analysis of 27 trials. Twenty of these trials supplied individual-patient data. No difference in survival was detected. The proportional reduction in the annual odds of death was 1.5% in favor of combination chemotherapy (95% CI, −8% to 5%; $P > 0.2$), with an odds ratio (OR) of 0.99 (CI, 0.93 to 1.05). An earlier literature-based meta-analysis (6) of 18 trials also failed to detect a survival difference between groups (OR, 1.04 [CI, 0.90 to 1.19]; $P > 0.2$). Two meta-analyses evaluated interferon for multiple myeloma. An overview of 24 randomized trials published in abstract form (8) demonstrated that interferon improved recurrence-free survival by 6 months and improved 3-year overall survival by 4%. Another meta-analysis (9) measured survival by a unique measure called the "mean lifetime survival." This meta-analysis found no difference in survival rate between the group receiving interferon and the group not receiving interferon (3.9 vs. 3.4 years, respectively; $P = 0.095$).

Table 1. **Evidence Included in This Practice Guideline Report**

Question	Studies Identified (References)
What is optimal standard-dose chemotherapy?	4 Meta-analyses (6–9)
In terms of survival, is peripheral blood stem-cell or autologous bone-marrow transplantation better than conventional chemotherapy?	2 Randomized trials (3, 4) 3 Nonrandomized comparisons (10–12) 1 Economic analysis (13)
What is the relative efficacy of autologous and allogeneic transplantation?	3 Nonrandomized comparisons (14–16)
What specifics of the transplantation process can be recommended?	6 Randomized trials (17–22) 4 Nonrandomized comparisons (23–26) 2 Noncomparative case series (27, 28) 2 Economic analyses (29, 30)
When should transplantation be performed?	1 Randomized trial (31)
Who should (or should not) receive a transplant?	2 Randomized trials (3, 4) 6 Nonrandomized comparisons (32–37) 2 Noncomparative case series (38, 39)

Guideline Recommendation. Multiagent chemotherapy or melphalan plus prednisone is appropriate therapy for a control group in a comparison of transplantation versus standard-dose therapy. The addition of interferon is unlikely to influence outcomes in the control group.

In Terms of Survival, Is Autologous Peripheral Blood Stem-Cell or Bone Marrow Transplantation Better than Conventional Chemotherapy?

We reviewed two randomized and three nonrandomized comparisons (Table 2). Attal and colleagues (3) randomly assigned 200 previously untreated patients younger than 65 years of age with stage II or III (40) myeloma to conventional chemotherapy or to a strategy that included autologous bone marrow transplantation. Patients were randomly assigned before therapy began. Conventional therapy consisted of 12 months of vincristine, melphalan, cyclophosphamide, and prednisone–

vincristine, carmustine, doxorubicin, and prednisone (VMCP–BVAP). Beginning with the ninth chemotherapy cycle, patients in this group received interferon, 3 million units/m^2 three times weekly. Patients randomly assigned to transplantation first received four to six cycles of VMCP–BVAP; patients who had a good performance status (World Health Organization performance status below grade 3), a serum creatinine level less than 150 μmol/L (<1.7 mg/dL), and an adequate bone marrow harvest collected after the fourth chemotherapy cycle received melphalan, 140 mg/m^2, and total-body irradiation, 800 cGy, followed by reinfusion of autologous bone marrow. After hematologic recovery, patients received interferon. The investigators analyzed the data on an intention-to-treat basis. Event-free and overall survival improved with autologous transplantation. In a subset analysis, this benefit appeared confined to patients younger than 61 years of age.

A second randomized trial (median follow-up, 56 months) assessed patients 55 to 65 years of age and was published in abstract form (4). The investigators detected no difference in event-free or overall survival between those receiving high-dose therapy and autologous bone marrow transplant and those receiving conventional VMCP. Three nonrandomized studies compared autologous bone marrow or peripheral stem-cell transplantation with matched (10, 11) or historical (12) controls receiving conventional therapy. All three reported superior outcomes in the patients undergoing transplantation.

A cost-effectiveness analysis using pooled data from published reports concluded that high-dose therapy with stem-cell reinfusion was cost-effective (13). The marginal cost increase associated with autologous transplantation was approximately $26 000 per life-year gained compared with conventional treatment.

Guideline Recommendation. When the DSG initially assessed this question, only the data from Attal and colleagues were available. The DSG agreed that the trial by Attal and colleagues was well conducted, but opinions varied about whether this evidence warranted a statement that autologous transplantation should be "recommended" or "offered" to specific patient groups. While remaining committed to principles of patient participation and autonomy in treatment decision making, there was consensus that the evidence supported transplantation as the "preferred" option and should be "recommended" to appropriate patients with stage II or III disease.

The DSG revisited this debate after receiving practitioner feedback on the draft recommendations. Nine respondents thought that one randomized trial provided insufficient evidence for the DSG to "recommend" stem-cell transplantation. They suggested that publication of the guideline be delayed until further evidence emerged or that the guideline be reworded to say that physicians should "offer" transplantation to appropriate candidates. After considering these options, the DSG again concluded that Attal and colleagues' study supporting the recommendation was well done and represented the "preferred" option.

After a literature search update located a second randomized trial (in abstract form) (4), the DSG again reconsidered its recommendation. The DSG concluded that while this trial was large and appeared well conducted, the nature of the publication (preliminary results reported in abstract form) was insufficient to cause a substantial change in the initial recommendations. However, as with the subset analysis performed by Attal and colleagues, which demonstrated that transplantation benefits were specifically identified in patients 60 years of age or younger, we recognized the potential for an interaction between age and treatment effect. The statement to "recommend" transplantation was thus re-

Table 2. **Comparison of Autologous Peripheral Blood Stem-Cell or Marrow Transplantation with Conventional Therapy**

Study (Reference), Report Type	Total Participants, *n*	Median Event-Free Survival*	Overall Survival*
Randomized, controlled trials			
Attal et al. (3), full paper	200	At 5 y, 28% vs. 10%; $P = 0.01$	At 5 y, 52% vs. 12%; $P = 0.03$
Fermand et al. (4), abstract	190	Median, 24.3 vs. 18.7 mo; $P = 0.07$	Median, 55.3 vs. 50.4 mo; $P > 0.2$
Nonrandomized comparisons			
Barlogie et al. (10), full paper	239	Not reported	At 5 y, 61% vs. 39%; $P = 0.01$
Lenhoff et al. (11), full paper	548	Median, not reached vs. 44 mo; $P < 0.01$	Not reported
Musto et al. (12), abstract	69	Median disease-free survival, 33 vs. 11 mo; $P < 0.02$	Median, 49 vs. 25 mo; $P < 0.03$

* Data reported as experimental (transplantation) group versus control group.

worded to indicate that the supporting data were strongest for patients younger than 55 years of age.

What Is the Relative Efficacy of Autologous and Allogeneic Transplantation?

No reported randomized trial has compared autologous with allogeneic transplantation. Table 3 summarizes three nonrandomized comparisons. The European Bone Marrow Transplant Registry (14) reported a case-control comparison of 189 patients receiving allogeneic sibling donor transplants and 189 patients receiving autologous stem-cell transplants. Median survival was superior with autologous transplantation. The treatment-related mortality rate was 41% with allogeneic transplantation compared with 13% with autologous transplantation ($P < 0.001$). Meanwhile, the relapse rate was higher in patients undergoing autologous transplantation (70% vs. 50% at 48 months; $P = 0.04$).

Table 3 also summarizes two smaller concurrent cohort comparisons (15, 16) from single centers. Neither report detailed the reasons for assignment to autologous or allogeneic transplantation. Varterasian and colleagues (15) detected no difference in median event-free or overall survival; Couban and colleagues (16) reported superior median survival for the group undergoing autologous transplantation.

Guideline Recommendation. Although comparative data are limited, survival appears superior with autologous transplantation. The DSG members unanimously decided to recommend autologous transplantation as the standard transplantation option. Two practitioners responded to this draft recommendation by indicating a potential future role of allogeneic transplantation. The DSG agreed that while ongoing clinical trials to improve allogeneic transplantation technology should be encouraged, autologous transplantation should be considered the present standard option.

What Specifics of the Transplantation Procedure Can Be Recommended?

Autologous transplantation is a complex procedure with several distinct components. We attempted to evaluate optimal pretransplantation chemotherapy, stem-cell source, role of stem-cell purging or selection, high-dose therapy regimen, single versus double transplant, and posttransplantation therapy.

Table 3. **Nonrandomized Comparisons between Autologous and Allogeneic Transplantation**

Study (Reference)	Patients Receiving Autologous Transplant	Patients Receiving Allogeneic Transplant	Median Survival*
	n		*mo*
Björkstrand et al. (14)	189	189	34 vs. 18; $P = 0.001$
Varterasian et al. (15)	24	24	33.5 vs. 38.6; $P > 0.2$
Couban et al. (16)	40	22	≥48 vs. 7; $P < 0.001$

* Data reported as autologous versus allogeneic transplantation.

Pretransplantation Chemotherapy

Pretransplantation chemotherapy could influence ultimate disease control; we identified no study assessing this question. Initial chemotherapy may also affect the ability to harvest sufficient stem cells and might therefore affect stem-cell engraftment (41). This concern has been suggested regarding melphalan use. In Attal and colleagues' study (3), patients received four to six cycles of alkylating agent–based chemotherapy (VMCP–BVAP) before bone marrow harvest. Ten percent of the patients in the transplantation group had insufficient harvests and could not receive the assigned transplant.

No randomized trial has assessed pretransplantation therapy. Two case series addressed the effect of cumulative alkylating agent exposure on stem-cell harvest quality (27, 28). Tricot and colleagues (27) performed a multivariate analysis of factors predicting engraftment in 225 patients with myeloma undergoing double autologous stem-cell transplantation. The end points of the study were time to platelet ($>50 \times 10^9$/L) and neutrophil ($>0.5 \times 10^9$ cells/L) engraftment; both were inversely correlated with alkylating agent exposure (for granulocytes, any exposure; for platelets, exposure for >1 month). Prince and colleagues (28) evaluated the effect of previous melphalan exposure on the ability to harvest stem cells in 54 consecutive collections of peripheral blood stem cells in 37 patients (28). Only 32% of patients receiving more than four courses of melphalan had collections meeting threshold values compared with 85% of those receiving zero to four courses ($P = 0.001$).

Guideline Recommendation. Previous exposure to alkylating agent may reduce the ability to harvest sufficient stem cells. A threshold melphalan dose that precludes successful harvesting has not been conclusively identified. Given these data and available alternatives, the DSG concluded that it is prudent to avoid exposure to melphalan before stem-cell collection when transplantation is a consideration. High-dose glucocorticoid-based regimens, such as vincristine, doxorubicin, and dexamethasone (VAD), are preferable for these patients.

Source of Stem Cells: Bone Marrow versus Peripheral Blood

The use of peripheral blood stem cells results in faster engraftment of neutrophils and platelets (42). Evidence suggests that using peripheral blood stem cells in patients with myeloma might reduce malignant cell contamination of the autograft (43). One randomized trial, which was reported in abstract form, described a comparison between bone marrow and peripheral blood as the stem-cell source in patients with myeloma (17). In that trial, 133 patients received peripheral blood stem cells and 89 received autologous bone marrow. Neutrophil engraftment was faster in patients receiving peripheral blood stem cells (9.7 vs. 12.2 days; $P < 0.001$). The study detected no difference in toxic deaths, response rates, or 2-year survival. Three nonrandomized studies reported comparisons of peripheral blood stem cells with autologous bone marrow (23–25); one of these studies included patients with breast cancer (25). Each study demonstrated faster engraftment with peripheral blood stem cells, and one trial also detected an advantage in transfusion needs, antibiotic use, and hospital days (25).

Two studies assessing economic end points have addressed this topic: Duncan and colleagues (29) performed a cost-minimization analysis to compare transplantation using peripheral blood stem cells with autologous bone marrow; Powles and colleagues (30) included data on cost in a nonrandomized comparison that assessed tolerance of post-transplantation interferon as the primary outcome. Both analyses demonstrated that peripheral blood stem-cell transplantation had economic advantages.

Guideline Recommendation. On the basis of differences in outcomes affected by engraftment rate, the DSG favored the use of peripheral blood stem cells as the stem-cell source.

Role of Stem-Cell Purging or Selection

The presence of malignant cells in harvested stem cells could contribute to disease recurrence. Investigators have attempted different methods to reduce malignant contamination. Stewart and colleagues (18) reported preliminary results of a randomized trial comparing outcomes in 93 patients receiving selected $CD34^+$ stem cells with the outcomes in 97 patients receiving unselected peripheral blood stem cells. Molecular testing showed that tumor contamination decreased with stem-cell selection. During a median follow-up of 37.2 months, the study detected no difference in survival ($P > 0.2$).

Guideline Recommendation. Insufficient data exist to recommend purging or stem-cell selection outside a clinical trial.

High-Dose Therapy Preparative Regimen

Two comparative trials—one randomized and one nonrandomized, both reported in abstract form (19, 26)—assessed the role of total-body irradiation. In a randomized trial comparing outcomes in newly diagnosed patients undergoing peripheral blood stem-cell transplantation, 113 patients received melphalan, 140 mg/m^2, plus total-body irradiation, and 108 received melphalan, 200 mg/m^2, alone (19). This study detected no difference in response rate or 2-year survival. Total-body irradiation was associated with longer durations of neutropenia and thrombocytopenia, increased red cell and platelet transfusion requirements, and more days of intravenous antibiotic therapy. Björkstrand and colleagues (26) analyzed data from the European Blood Marrow Transplantation Registry for 1905 patients who underwent autologous transplantation for myeloma. Regimens that included total-body irradiation were associated with an inferior survival rate.

Guideline Recommendation. In the randomized trial demonstrating a benefit for autologous transplantation compared with conventional-dose chemotherapy (3), the conditioning therapy received by transplant recipients included total-body irradiation. The DSG therefore initially considered this regimen to be the standard of care outside a clinical trial. On the basis of preliminary results of the above two studies reported in abstract form, the DSG concluded that either high-dose melphalan, 200 mg/m^2, alone

Table 4. **Comparison of Single versus Double (Tandem) Transplantation of Autologous Peripheral Blood Stem Cells or Marrow**

Study (Reference), Report Type	Total Participants, *n*	Median Event-Free Survival*	Overall Survival*
		%	
Randomized, controlled trials			
Attal et al. (20), abstract	402	At 3 y, 31 vs. 39; *P* value not significant	At 3 y, 58 vs. 66; *P* value not significant
Tosi et al. (21), abstract	192	Data not provided; *P* value not significant	At 2 y, 90 vs. 90; *P* value not significant
Nonrandomized comparison			
Bjökstrand et al. (26), abstract	1530	Data not provided; progression-free survival superior with double transplants	Data not provided; between-group differences not significant

* Data reported as single versus double transplant.

or melphalan, 140 mg/m^2, with total-body irradiation could be considered standard therapy.

Single versus Double Transplants

Three studies—two randomized trials (20, 21) and one nonrandomized comparison (26)—assessed the role of double autologous transplantations performed in succession; these data, which were published in abstract form, are shown in Table 4. This therapy, called "tandem transplantation," includes a planned second transplant following recovery from a first transplantation. This practice is in contrast to performing a second transplantation after disease progression following a first transplantation. Both randomized studies failed to detect a difference in event-free or overall survival. In one of the three studies (26), a secondary analysis of the patients who received a second transplant demonstrated prolonged relapse-free and event-free survival (P = 0.03) for patients receiving tandem transplants. A nonrandomized comparison of data submitted to the European Bone Marrow Transplant Registry demonstrated superior progression-free survival in the patients undergoing tandem transplantation (data points not reported); the study detected no survival difference (21).

Guideline Recommendation. Comparative trials are susceptible to selection bias when outcomes of patients who actually receive a second transplant are compared with those who received a single transplant. Randomized trials analyzed on an intention-to-treat basis are needed to address this question. The DSG concluded that the current data do not support the standard use of tandem transplants.

Post-transplantation Therapy

Because transplantation appears noncurative, maintenance therapy, such as with interferon, may be used in an attempt to improve disease control and survival. In the randomized comparison of transplantation with conventional-dose chemotherapy (3), both groups received interferon until disease progression. It is not possible to factor out the contribution of this agent to the success of the high-dose treatment strategy. Two comparative trials tested use of maintenance interferon after autologous transplantation.

Cunningham and colleagues (22) reported outcomes in 84 patients randomly assigned to interferon, 3 million units three times weekly until disease progression, or to no maintenance therapy. The data suggested a trend toward prolonged progression-free survival in the interferon group (median, 48 vs. 27 months; P = 0.11); the study found no difference in survival. A nonrandomized comparison assessing data from 1905 patients on file with the European Bone Marrow Transplant Group demonstrated that post-transplantation interferon as maintenance treatment was associated with prolonged survival (21).

Guideline Recommendation. The evidence for benefit of interferon is conflicting, and the DSG could not reach a consensus on this issue. Some DSG members considered interferon to be an essential part of the therapeutic plan described by Attal and coworkers (3); these members believed that deleting this component could result in inferior outcomes. Other members believed that without data from randomized trials demonstrating a survival advantage, the toxicity of this agent precludes routine use.

When Should Transplantation Be Performed?

In the randomized trial demonstrating superior event-free and overall survival in patients receiving an autologous transplant (3), bone marrow was harvested early after diagnosis and transplantation was performed at a median of 5.5 months after therapy began. One randomized trial compared early with late autologous transplantation in patients with stem-cell collection shortly after commencing therapy (31); among 202 patients, 185 were randomly assigned to receive an autologous transplant as part of initial therapy or upon disease progression. In an intention-to-treat analysis, disease progression was delayed in the 91 patients receiving early transplantation compared with the 94 patients assigned to late transplantation (median event-free survival, 39 months [CI, 29 to 48 months] vs. 13 months [CI, 9 to 18 months]; *P* value not reported). However, no difference in median survival between the groups was detected (64.6 vs. 64.0 months; $P > 0.2$). Time without symptoms, treatment, and treatment toxicity (TWISTT) was 27.8 months (CI, 23.8 to 31.8 months) for the early transplantation group and 22.3 months (CI, 16.0 to 28.6 months) for the late transplantation group.

Guideline Recommendation. Although delaying transplantation until disease progression in patients who have stem cells collected shortly after therapy initiation does not adversely affect survival, it may decrease the time without symptoms of myeloma or treatment toxicity without a clear potential for benefit. The DSG believed that transplantation as part of initial therapy was potentially advantageous; patients need to be counseled to determine individual preferences. The need for early stem-cell harvesting deserves emphasis because no comparative data indicate the efficacy of harvesting stem cells during disease progression.

Who Should (or Should Not) Receive a Transplant?

Age

Age has been used as a proxy measure to determine the safety of performing autologous transplantation. A commonly stated upper-age threshold is 65 years. However, several reports described transplantation in older patients (32–36, 38, 39). The DSG identified two randomized trials and three nonrandomized comparisons addressing patient age. The study by Attal and colleagues comparing high-dose with standard-dose therapy enrolled patients up to 65 years of age (3); 42% of patients age older than 60 years did not complete the transplantation compared with 18% of patients 60 years of age or younger ($P = 0.01$). In a subset analysis based on intention to treat, transplantation was superior to standard-dose therapy in patients 60 years of age and younger, with no benefits detected in patients older than age 60 years. A second randomized trial comparing transplantation with conventional therapy in patients 55 to 65 years of age was reported in abstract form (4); this study failed to detect a difference in event-free or overall survival. Two case–control studies (34, 35) and one cohort study (36) have reported that patients older than 65 years of age can safely receive an autologous transplant, with no differences in outcomes detected between the older and younger patients.

Guideline Recommendation. The DSG had already concluded that data supporting autologous transplantation were strongest for patients younger than 55 years of age. Although transplantation may be safely performed in older patients, improvements in event-free and overall survival have only been documented in randomized trials for patients up to 60 years of age. Because age may be a proxy measure for aspects of disease biology, other comorbid illness, and treatment tolerance, physicians must use clinical judgment in recommending transplantation to patients older than 60 years of age.

Renal Function

The randomized trial supporting use of autologous transplantation over standard-dose therapy (3) included patients with renal dysfunction but with a serum creatinine level correcting to less than 150 μmol/L (<1.7 mg/dL) before transplantation. In patients with significant renal dysfunction, transplant-related toxicity may be greater, and the magnitude of benefits compared with those of standard-dose treatment might therefore be reduced. One case–control study (37) of 42 patients with a serum creatinine level greater than 200 μmol/L (>2.26 mg/dL) demonstrated that treatment toxicity was greater in patients with renal dysfunction; the observed difference in 3-year survival in patients with renal dysfunction versus controls was not statistically significant (44% vs. 59%; $P = 0.15$).

Guideline Recommendation. Although autologous transplantation is feasible in patients with serious renal dysfunction, whether these patients actually benefit from the treatment is unclear. Randomized data showing benefits for transplantation have been limited to patients with a serum creatinine level less than 150

μmol/L (<1.7 mg/dL); interpretation of the case–control study is limited by the study design and the small sample size. The DSG concluded that transplantation could not be recommended as standard therapy for patients with a creatinine level greater than 150 μmol/L (>1.7 mg/dL) until randomized trials can demonstrate a survival benefit for these patients. Renal dysfunction seen at diagnosis may improve with initial therapy for myeloma; these patients should be subsequently considered for high-dose therapy.

CONCLUSIONS

The Hematology DSG of the CCOPGI developed the guidelines presented here, which assess the role of stem-cell transplantation for patients with myeloma. These guidelines will be reviewed and updated every 6 months. Their recommendations are as follows:

1. Autologous transplantation is recommended for patients with stage II or III myeloma and good performance status. The evidence is strongest for patients younger than 55 years of age and a serum creatinine level less than 150 μmol/L (<1.7 mg/dL) after hydration and remission-inducing chemotherapy. Physicians must use their clinical judgment in recommending transplantation to other patients.

2. Allogeneic transplantation is not recommended as routine therapy.

3. Patients potentially eligible for transplantation should be referred for transplant assessment early after diagnosis and should not receive extensive exposure to alkylating agents, such as melphalan, before collection of stem cells. High-dose glucocorticoid-based regimens, such as VAD, are preferable for these patients.

4. Harvesting of autologous peripheral blood stem cells should be performed early in the patient's treatment course. Best available data suggest that transplantation is most advantageous when performed during initial therapy.

5. Comparative data regarding the specifics of the transplantation process are insufficient to allow definitive recommendations. In the absence of such data, the use of a single transplant with high-dose melphalan, 200 mg/m^2, alone or melphalan, 140 mg/m^2, with total-body irradiation is suggested for patients undergoing transplantation outside of a clinical trial.

6. At this time, no conclusions can be reached about the role of interferon following transplantation.

Note added in proof: These guideline recommendations are based on work completed in March 2001. New information necessitates that practice guidelines undergo regular updating. Based on a recent publication (44), the Hematology Site Group of the Cancer Care Ontario Practice Guidelines Initiative now recommends that when patients with multiple myeloma undergo autologous transplantation, standard pretransplantation therapy should consist of melphalan, 200 mg/m^2. Please see the Web site of the Cancer Care Ontario Practice Guidelines Initiative (www.cancercare.on.ca/ccopgi/) for updated recommendations.

APPENDIX: MEMBERS OF THE HEMATOLOGY DISEASE SITE GROUP OF THE CANCER CARE ONTARIO PRACTICE GUIDELINES INITIATIVE

The following members contributed to this guideline: R. Meyer (*Chair*), H. Abu Zahra*, Ms. L. Baig*, I. Chin-Yee, Ms. B. Costello*, R.M. Crump, C. deMetz, H. Dhaliwal*, Ms. R. Esmail, P. Galbraith*, S. Gluck*, M. Gospodarowicz, L. Huebsch, K. Imrie, Mr. M. Kacsor, L. Kaizer, C.T. Kouroukis, J. MacEachern, J. Matthews, J. Meharchand, H. Messner, C. Sawka*, N. Shehata, A. Smith, I. Walker, and K. Yee.

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A complete list of current Disease Site Group members is available on the Web site of the Cancer Care Ontario Practice Guidelines Initiative at www.cancercare.on.ca/ccopgi/.

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LETTERS

Osteoarthritis and Knee Pain

TO THE EDITOR: Felson and colleagues reported that self-reports of knee pain correlated highly with increased intraosseous water in the distal femur and proximal tibia on magnetic resonance imaging (1). Although their study is a useful contribution to the literature, it raises several concerns.

The authors did not distinguish between focal fluid collections in subchondral cysts and the more diffuse lesions described as "marrow edema." Therefore, the same cysts used in the staging of osteoarthritis on plain radiographs presumably counted as marrow lesions on magnetic resonance imaging. It seems appropriate to ask whether the different lesions of "cysts" and "edema" correlate differently with pain.

Although any osteophyte was sufficient to classify a knee as osteoarthritic, joint space narrowing was assessed carefully but was not reported. Some or most pain-free patients could have had normal cartilage thickness with incidental osteophytosis (2). If so, they would not seem to be appropriate controls.

Some of the patients were recruited by newspaper advertisements, and none were examined. Therefore, the sample probably included patients with pain in the anserine bursae (classic tender points for fibromyalgia) or the patellae; this makes it difficult to correlate reported knee pain with femoral and tibial findings.

Felson and colleagues cited the classic study by Arnoldi and coworkers (3), which emphasized the relationship between intraosseous hypertension and the deep aching pain at rest that is often aggravated by preceding joint usage. However, because Felson and colleagues did not evaluate pain patterns, it is difficult to determine how the two studies "may be related."

Felson and colleagues also mention the comparable marrow edema reported with traumatic contusions, osteonecrosis, and transient painful osteoporosis. Findings may be similar in inflammatory joint diseases, stress fractures, complex regional pain syndromes, and other bone and joint afflictions. In all of these conditions, the central finding is a focal increase in the water signal within bone. However, the volume of any bone is fixed by its mineralized shell. This means that any volumetric increase in one constituent must come at the expense of another, that is, bone contents obey zero-sum principles. When the water content of epiphysial bone increases, fat is depleted. Perhaps it is time to consider the contribution of fat to normal epiphysial mechanics, to examine how fat leaves and where it goes, and to study the possible role of fat depletion in osseous pain.

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IN RESPONSE: To respond to the questions posed, first, we did not count any cysts as marrow edema lesions, even though cysts are often contained within these lesions. We scored edema lesions alone.

Second, the consensus way of defining osteoarthritis, according to the American College of Rheumatology (1) and to a large number of epidemiologic studies (2), is to use osteophytosis as the criterion. Joint space narrowing, although carefully assessed in our study, can be hard to characterize definitively and may sometimes represent thinning cartilage caused by age and not disease. We believe our definition of osteoarthritis as osteophytosis is appropriate.

Third, the assertion that none of the patients in our study were examined is incorrect. In fact, all of the patients were examined. Those who did not have knee osteoarthritis were excluded. Many patients with physical and radiographic evidence of clinical osteoarthritis have patellar pain and pain in the anserine area; these findings would not necessarily have excluded patients.

Fourth, pain at rest was uncommon in our sample, as it is in most patients with osteoarthritis. Most of our participants had pain on activity, such as walking up and down stairs or walking long distances on level ground. Our findings suggest that even those symptoms, not just pain at rest, are probably related to lesions characterized by bone marrow edema.

Fifth, Dr. Simkin presents an interesting hypothesis regarding fat depletion and its relation to bone pain. Arnoldi and coworkers (3) hypothesized that the pain of osseous hypertension was caused more by the increased pressure inside the bone than by any depletion of elements within it.

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Pseudoaccountability

TO THE EDITOR: Kassirer (1) writes that efforts by the medical profession to self-regulate its practices have been poor and uneven; he suggests turning the job over to an independent, disinterested, and outside group. Our experience with self-regulation leads us to a different conclusion.

The Palo Alto Medical Clinic is a multispecialty clinic with 240 physicians. To assure ourselves and the public that we provide the highest possible quality of care, we have established the following committees. Department heads and the professional affairs committee examine the work of each physician every 1 to 2 years by reviewing charts and questioning colleagues. Complaint files and incident reports are surveyed monthly. Each clinic physician meets with the chairperson of the professional affairs committee every 2 years, or more often if necessary after the annual or biannual review is concluded. The care review committee collects and disseminates information about medical errors in diagnosis, treatment, or preventive care. Reviewers meet with the involved physician in open discussion. Teaching points are then distributed throughout the clinic by e-mail and other presentations. The physician well-being committee monitors the emotional and physical health of all physicians. Anonymous concerns about burnout, drug or alcohol abuse, or any other illnesses are dealt with immediately. A full-time, nonphysician employee works closely with the above committee and is responsible for quality assurance throughout the clinic. He reports directly to the executive board.

With a nonthreatening environment, vigorous leadership, a nononsense approach, and the common goal of high standards, we feel physicians can "self-regulate, self-monitor, and self-discipline" each other.

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Long-Term Prediction of Coronary Heart Disease in Young Men

TO THE EDITOR: Navas-Nacher and colleagues (1) discussed the impact of risk factors (age, serum cholesterol level, systolic blood pressure, and cigarette smoking) for coronary heart disease (CHD) on men 18 to 39 years of age. They found a significant association between these risk factors and death from CHD over 20 years.

The authors described measuring plasma glucose levels in the 11 016 participants. However, they did not report plasma glucose levels at baseline and apparently did not explore the association between glycemia and cardiovascular mortality. We would like to know whether a significant association existed between plasma glucose levels and death from CHD in these young men. We are also interested in the contribution of plasma glucose levels to a risk model including the classic risk factors for cardiovascular death, since the available evidence is inconsistent. Data from the Whitehall study (2) and the Framingham cohort (3) showed that excess risk for CHD occurred only at levels of glycemia compatible with the diagnosis of diabetes. However, a meta-regression analysis of more than 95 000 persons over 12 years (4) and the EPIC-Norfolk cohort of more than 4500 men (5) revealed that glycemia and glycosylated hemoglobin concentration, respectively, predicted mortality at levels below the diagnostic threshold for diabetes.

Navas-Nacher and colleagues contribute knowledge about the role of traditional risk factors in predicting cardiovascular risk in young men. In addition, data from this study could provide additional evidence about the less certain association between impaired fasting glucose and CHD in this population.

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IN RESPONSE: Gami and colleagues correctly note that we measured plasma glucose following a 50-g oral glucose load, as described elsewhere (1). We also evaluated serum cholesterol, blood pressure, cigarette smoking, weight, height, electrocardiographic data, education, and ethnicity. The primary goal of our analysis was to determine whether traditional CHD risk factors differed between young and middle-aged men in follow-up for long-term mortality. To answer Gami and colleagues' question concerning asymptomatic glycemia and long-term CHD mortality, we included plasma glucose level (in increments of 1.11 mmol/L [20 mg/dL]) in the multivariate models we originally reported (Table). After adjustment for major covariates, plasma glucose level and 20-year CHD mortality had a border-

Table. **Relative Risk for Death from Coronary Heart Disease within 20 Years**

Variable	Relative Risk (95% CI)		*P* Value
	Young Men	Middle-Aged Men	
Age (per 6-year increase)	1.59 (1.25–2.01)	1.58 (1.45–1.73)	>0.2
Serum cholesterol level (per 1.04-mmol/L [40-mg/dL] increase)	1.96 (1.68–2.30)	1.18 (1.12–1.25)	<0.001
Systolic blood pressure (per 20–mm Hg increase)	1.33 (1.07–1.66)	1.27 (1.18–1.36)	>0.2
Diastolic blood pressure (per 10–mm Hg increase)	1.23 (1.04–1.46)	1.24 (1.17–1.32)	>0.2
Cigarettes smoked per day (per 10-cigarette increase)	1.36 (1.21–1.53)	1.25 (1.19–1.31)	0.16
Body mass index (per 4-kg/m^2 increase)	1.02 (0.83–1.25)	1.03 (0.94–1.12)	>0.2
Major electrocardiographic abnormalities	0.84 (0.31–2.28)	2.73 (2.25–3.30)	0.02
Minor electrocardiographic abnormalities	1.25 (0.67–2.35)	1.51 (1.16–1.96)	>0.2
Education (per 3-year increase)	0.69 (0.55–0.86)	0.79 (0.73–0.87)	>0.2
Black ethnicity	0.52 (0.21–1.29)	0.92 (0.65–1.30)	>0.2
Plasma glucose level (per 1.11-mmol/L [20-mg/dL] increase)	1.01 (0.93–1.11)	1.03 (1.00–1.06)	>0.2

line relationship in middle-aged men (relative risk, 1.03 [95% CI, 1.00 to 1.06]) and were not significantly related in men who were 18 to 39 years of age at baseline. However, no significant difference was seen in CHD risk between the two age groups because of overlapping confidence intervals ($P > 0.2$).

A previous report from this cohort (1) examined black and white men who were 35 to 64 years of age at baseline. Elevated postload glucose level was significantly related to total death from cardiovascular disease in 22-year follow-up in this more heterogeneous, and mostly older, group of men. These results were among those compiled for the meta-regression analysis (2) mentioned by Gami and colleagues.

Long-term prediction of CHD based on single glucose measurements in asymptomatic nondiabetic patients has produced inconsistent results, both within and between studies (2). However, our primary purpose was to determine and raise awareness of the long-term consequence of major CHD risk factors that are already present in young adulthood. Perhaps the greatest hope for elimination of CHD as an epidemic in western societies is prevention of the risk factors themselves. Data on asymptomatic glycemia and CHD risk are inconsistent. However, prevention of high cholesterol levels, high blood pressure, cigarette smoking, and overweight involves attention to healthy behaviors and to regular exercise—the same measures that can prevent glucose intolerance and diabetes (3). Gami and colleagues are therefore correct in drawing attention to factors associated with asymptomatic glycemia in the long-term prevention of CHD.

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Appropriate Antibiotic Use for Acute Pharyngitis

TO THE EDITOR: We congratulate the Centers for Disease Control and Prevention, the American Academy of Family Physicians, and the American College of Physicians–American Society of Internal Medicine for their clear position paper on antibiotic use for acute pharyngitis in adults (1). These honorable organizations found a good balance between the risks for untreated group A β-hemolytic streptococcal pharyngitis and the risks posed by unnecessary use of antibiotics (side effects, microbial resistance, medicalization).

To our surprise, one recommended treatment strategy appeared to be almost identical to the guidelines in the Netherlands: to refrain from any microbiological test and to limit antibiotic therapy to patients with three or four of the so-called Centor criteria. This suggests that a traditionally strong microbe-oriented approach is gradually shifting toward a more patient-oriented approach. One explanation for this change could be that in many western communities, prevention of acute rheumatic fever is no longer the main reason to administer penicillin because of the low incidence of the condition.

In a previous study, we found that within 1 week, most patients with group A β-hemolytic streptococcal pharyngitis recovered while receiving placebo (2). This finding supports the attention that the guideline authors paid to the natural defense mechanisms of the host. Immunocompetent hosts in primary care interact adequately with potentially virulent microbes, without the need of antimicrobial support. However, we do not know which patients with pharyngitis really benefit from antibiotics. In our primary care–based case–control study, we isolated not only high-colony-count group A streptococci from all patients age 15 to 44 years who met at least three of the four Centor criteria (45.5%) but also high-colony-count group C and group G streptococci (14.4%) (3). All three subtypes were associated with active disease, and penicillin accelerated recovery in all of these patients (2–4). Today, microbiological tests do not detect seriously ill patients with pharyngitis not caused by group A streptococci, but they do identify carriers and mildly ill patients who will not benefit from penicillin. Until better tests are developed, the guidelines for primary care physicians should focus on the clinical picture of the host rather than on the presence of the microbe.

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IN RESPONSE: We thank Drs. Zwart and Sachs for their interest in our paper. We largely agree with the overall tenor of their comments. However, we do not believe that any good evidence supports a benefit from administering antibiotics to patients with non–group A streptococcal pharyngitis. In Zwart and colleagues' study (1), the results are neither clinically nor statistically compelling; indeed, in the Discussion section of that paper, the authors are (appropriately) much more cautious about non–group A streptococci than they are in their letter. We are therefore not convinced of the need for "better tests" to identify such infections.

With regard to testing in a more global sense, we tried to have our recommendations reflect the tradeoffs between a test-and-treat strategy and a strategy consisting entirely of empiric treatment of pharyngitis based on the validated clinical score described by Centor. We agree with Zwart and Sachs and the authors of another recent review (2) that this clinical screen provides an excellent basis for decision making. The particular test-and-treat strategy that we also recommended as an alternate appropriate approach is likely to lead to antibiotic treatment of somewhat fewer patients *without* group A streptococcal pharyngitis than will the purely empiric strategy; however, this will come at the cost of testing a very large number of patients. It will also result in failure to treat some highly symptomatic patients with group A streptococcal pharyngitis who have a false-negative result on a rapid antigen screening test. We believe that available evidence supports either of these strategies as reasonable and as justifiable in current clinical practice.

Finally, we stress that all evidence-based guidelines should be reevaluated periodically and revised as appropriate in the light of new information. If new evidence convincingly demonstrates the value of identifying and treating non–group A β-hemolytic streptococcal infections, it should certainly be incorporated into future guidelines.

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Cardiovascular Outcomes and Renal Disease

TO THE EDITOR: Mann and coworkers (1) reported on the independent association between baseline renal insufficiency (serum creatinine level, 124 to 200 μmol/L [1.4 to 2.3 mg/dL]) and cardiovascular outcomes in the Heart Outcomes and Prevention Evaluation (HOPE) study. Although the Discussion section of the paper focuses on the pathophysiologic reasoning for why renal insufficiency may accelerate atherosclerosis, the authors have missed the larger picture of "cardiorenal risk" (1).

We believe that there are four explanations for poor outcomes in patients with renal insufficiency: 1) excess and incompletely controlled confounding of conventional risk factors, 2) therapeutic nihilism, 3) complications from conventional therapies and procedures, and 4) special biological features of the renal failure state that promote atherosclerosis, heart failure, arrhythmias, and valvular disease. Mann and coworkers' study could not touch on these factors because most of them occur during hospitalization for cardiovascular events (2). We and others have shown the mathematical risk for acute renal failure that requires dialysis and for subsequent mortality after acute coronary intervention and bypass surgery in patients with renal insufficiency (3–5). In addition, we recently demonstrated lower rates of therapy with thrombolytics, primary angioplasty, and β-blockers in patients with renal insufficiency (5). These and other factors produce the results demonstrated by Mann and colleagues' study and those seen in clinical care. Although we agree with the authors that accelerated atherosclerosis is a central feature of cardiorenal risk, we encourage the clinical and research community to consider the issue in broader terms based on published observations.

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IN RESPONSE: McCullough and colleagues correctly point out that patients with even mild renal insufficiency exhibit an excess of cardiovascular risk factors. Controlling for such risk factors indicated that renal insufficiency is an additional, independent risk factor. This is also evident from Table 1 of our article. Therapeutic nihilism was obviously not a problem of the HOPE study because antiplatelet, blood pressure–lowering, and cholesterol-lowering agents were, if anything, more frequently administered in patients with renal insufficiency than those without.

However, we emphasize that the results of the HOPE study contradict the common practice to withhold angiotensin-converting enzyme inhibitors, including ramipril, in patients with renal insufficiency. We have no evidence that patients with renal insufficiency in the HOPE study received fewer thrombolytics; invasive procedures, including revascularization (a secondary outcome of the HOPE study); or β-blockers. It is entirely possible that risk factors we did not evaluate may explain some of the increased risk associated with even mild renal insufficiency. However, current experimental and clinical evidence indicates that some aspects of renal failure may promote atherosclerosis and may be treatable. Further research into these factors is necessary, and our article was published to stimulate such investigations.

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William of Occam and Occam's Razor

TO THE EDITOR: Attributed to the 14th-century English philosopher and theologian William of Ockham (simplified to "Occam" by medieval spelling), Occam's razor is a logical device used by physicians to identify the single best cause of a patient's constellation of symptoms (1, 2). Most clinicians know very little about Occam and the origin of the principle that bears his name.

William was born in 1285 in Ockham, England. As a youngster in the Franciscan order, he studied logic (3). Subsequently, he studied theology at Oxford University (3). He lectured on theological works, using his passion for logic to identify inconsistencies in Catholic Church teachings. Such heretical views resulted in his expulsion from the university in 1319 and a presence before Pope John XXII in Avignon, France, in 1324 (3).

Occam fled from Avignon in 1328 and was subsequently excommunicated. He traveled to Pisa to ask the German Emperor, Ludwig IV of Bavaria, for sanctuary, reportedly pleading, "Emperor, defend me with your sword, and I will defend you with my pen" (4). Persuaded by this argument, Ludwig brought Occam to Munich, where the great philosopher–logician served until his death in 1349 (3).

Occam held firmly to the philosophical principle that one should not look for multiple causes of any effect if a single cause can provide a suitable explanation. Referred to as the Law of Parsimony, Occam effectively used this principle to cut away at the ideas of rival thinkers. In 1812, German historian Wilhelm Gottlieb Tennemann was the first to recognize Occam's frequent use of the device (5). English historian William Hamilton then appropriately named the Law of Parsimony "Occam's razor" in 1852, pointing out that Occam wielded it sharply in his arguments (5). Occam's razor is a helpful tool for physicians, although its use can be limited in some clinical syndromes, which reflect multiple independent disorders that cannot be reduced to a single, parsimonious root cause.

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Correction: Cost-Effectiveness of Statins in Older Patients with Myocardial Infarction

TO THE EDITOR: During further work with our model of the cost-effectiveness of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor ("statin") therapy in older patients with myocardial infarction (1), we discovered an error in one aspect of the model presented. This error does not change the paper's conclusion but alters some of the results presented. In Table 1 of the article, the base-case risk ratio for death from all causes other than myocardial infarction and stroke should be 1.03, not 1.52. Rerunning the model with this new base-case value results in mean undiscounted life expectancies of 6.78 and 7.40 years, respectively, for patients in the usual care and statin strategies; discounted, quality-adjusted life expectancies become 5.06 years for patients in the usual care strategy and 5.48 years for patients in the statin strategy. Costs should be $3798 and $9519 for the usual care and statin strategies, respectively. The incremental cost-effectiveness of statin therapy in comparison to usual care is now $13 700 per quality-adjusted life-year gained. Correction of these data results in a cost-effectiveness ratio still more favorable to statin therapy than initially reported, and our conclusions on the cost-effectiveness of statins in older patients with previous myocardial infarction remain unchanged.

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BOOK NOTES

Structured abstracts of information on newly published books, computer programs, selected Web sites, and other material are provided in this portion of Medical Writings. "Order phone" numbers can be used to place orders directly with publishers.

Sexual Chemistry: A History of the Contraceptive Pill

Marks LV. 359 pages. New Haven: Yale Univ Pr; 2001. $29.95. ISBN 0300089430. Order phone 203-432-0960.

Field of medicine: Reproductive health, medical history, and women's studies.

Format: Hardcover book.

Audience: Women's health care providers, medical historians, and consumers.

Purpose: To provide a comprehensive history of the oral contraceptive pill and its interplay with science, medicine, technology, and society.

Content: Chapter 1 describes the population problem and neo-Malthusian and eugenics movements of the Cold War era. The author recounts the chemical evolution of the pill and then discusses the original human trials and the approval of Enovid in 1960. Chapter 5 examines the response of physicians to the introduction of the pill. Although the initial trials and regulatory approval of the pill have since been criticized, Marks explains that the trials were more than sufficient according to the knowledge and ethical standards of the time. Chapters 6 and 7 explore the pill's reported association with thrombosis and cancer and how these conditions affected women, government policy, and epidemiologic research. In chapter 8, Marks disputes accounts describing the pill as the product that led to the sexual revolution. She explains how the pill's effects were much more diverse; for example, the pill gave married women freedom from incessant childbearing. Marks explores the debate in the Catholic Church regarding the "naturalness" of the pill, and she concludes with a summary of contraceptive pill use around the world, and how its adoption was complicated by social, political, and economic factors in addition to science.

Highlights: The book is well researched and thorough. Marks interweaves material from personal interviews, medical literature, and historical archives in a captivating synopsis. She also includes detailed reference material for those interested in further reading, as well as illuminating graphics.

Limitations: The discussion of controversial issues such as the health risks associated with the oral contraceptive pill is a hodgepodge of anecdotes, scientific research, and opinion. Furthermore, the health benefits of the pill are given short shrift.

Related reading: Djerassi's *This Man's Pill: Reflections on the 50th Birthday of the Pill* covers the history of the oral contraceptive pill, but in a self-centered way. Asbell's *The Pill: A Biography of the Drug That Changed the World* (Random House, 1995) is similar but does not read as well. McLaughlin's *The Pill, John Rock, and the Church: The Biography of a Revolution* (Little, Brown; 1982) is for those interested in the theological aspects of the pill.

Reviewer: Kavita Nanda, MD, MHS, Family Health International, Research Triangle Park, North Carolina.

Managing Death in the ICU: The Transition from Cure to Comfort

Curtis JR and Rubenfeld GD, eds. 388 pages. Oxford: Oxford Univ Pr; 2001. $59.95. ISBN 0195128818. Order phone 800-451-7556.

Format: Hardcover book.

Audience: Clinicians who work in intensive care units (ICUs), including physicians, nurses, respiratory therapists, and hospital chaplains; bioethicists; and legal scholars who seek a clinical perspective on end-of-life care in ICUs.

Purpose: This book offers a comprehensive, contemporary perspective on palliative and terminal care in ICUs, with focus on practical issues of decision making, problem solving, and clinical management.

Content: Multiauthor book composed of 28 chapters in five parts. The book begins with an introduction to recent changes in the management of death in ICUs. The second part reviews the role of prognosis, personal values, and medical advanced planning in decisions to limit life support. The core chapters in part 3 provide specific advice on management of death in ICUs, with emphasis on various participants, including physicians, nurses, patients, and family members. Part 4 reviews cultural, legal, economic, and organizational considerations in end-of-life care. A survey of terminal care for patients who have specific diseases, children, and elderly patients concludes the book.

Highlights: No musing by pipe-smoking, armchair philosophers here: This book was edited and written by applied scholars who have personal experience caring for terminally ill patients in ICUs. A variety of personal perspectives is presented, yet the book is largely evidence-based and thoroughly referenced to recent scientific literature. Clinicians wanting the "know how" will find this book a useful avenue to the accumulated wisdom of those who have traveled the path before.

Limitations: Several topics important to clinicians are lightly covered or omitted. The book offers little practical advice on the determination of competence or decision-making capacity. Conflicts within families and between family members and clinicians are extraordinarily important to end-of-life care in ICUs; there is limited advice on dealing with these conflicts. Readers seeking specific information on the views of various religious and ethnic groups regarding end-of-life care must look elsewhere. Care of the body and the delicate issue of seeking consent for autopsies are covered only in passing. A chapter on quality-improvement surveying of families regarding the terminal care of their loved one would have been useful.

Related reading: Pace and McLean's *Ethics and the Law in Intensive Care* (Oxford Univ Pr, 1996).

Reviewer: John Hansen-Flaschen, MD, University of Pennsylvania, Philadelphia, Pennsylvania.

Intimate-Partner Violence: The Need for Primary Prevention in the Community

Intimate-partner violence is a serious problem, but it may be even more common than was previously believed. A 1999 report estimated that one third of women worldwide have been victims of intimate-partner violence (Heise L, Ellsberg M, Gottemoeller M. Ending Violence against Women. Population Reports. Baltimore: Johns Hopkins School of Public Health; 1999). Intimate-partner violence is the leading cause of injury to women 15 to 44 years of age—more common than automobile accidents, muggings, and rapes combined (The National Coalition against Domestic Violence Fact Sheet: Domestic Violence Is Under Reported. Office of the U.S. Surgeon General; 1 January 1994).

Abuse has been linked to gastrointestinal disorders, chronic pain syndromes, problem pregnancies, and substance abuse. In their most recent violent incident with an intimate partner, 39% of female victims sustained an injury and approximately one third of those required medical care. In the United States, about 1.5 million women each year are raped, physically assaulted, or both by an intimate partner (Tjaden P, Thoennes N. Prevalence, Incidence, and Consequences of Violence against Women: Findings from the National Violence against Women Survey. U.S. Department of Justice; November 1998).

PREVENTION

Vast resources have been channeled into tertiary prevention of intimate-partner violence, to the exclusion of primary prevention (Glossary). "I think it's been a real lost opportunity to perhaps prevent a health problem from materializing," commented Lori Heise, director of Women's Health Exchange (a nonprofit research and advocacy group for international health policies and practice in Washington, D.C.). She explained that despite major strides made in recent years to address intimate-partner violence, treatment of the victims has been the primary focus. In the 1970s, advocates for women's rights, she said, played a major role in shaping the trend toward tertiary prevention because treatment for female victims presented the most urgent need; consequently, primary prevention efforts received little attention.

Health care continues to place little emphasis on addressing the batterer, although it has played an increasingly important role in tertiary and secondary prevention efforts. For example, as recently as 5 years ago, physicians seldom inquired about intimate-partner violence during routine office visits and in questionnaires, whereas now questions about domestic violence are almost commonplace. Yet, such questions are aimed almost exclusively at female patients. Health care had mostly neglected to question men to see if they were at risk for committing violence. This is only now beginning to change. In visiting more than 20 countries over 10 years for her report "Ending Violence against Women," Heise discovered that universally—especially in the United States—male batterers and primary prevention have been ignored.

A COMMUNITY CULTURE OF VIOLENCE

Traditionally, U.S. communities did not get involved until after the violence became a law-enforcement issue. "Years ago, there was more thinking that this was a domestic dispute, and therefore, it is something that is handled within a family. But people are starting to recognize that this isn't just the victim's problem—this is a problem to society," asserted Annmarie Kaiser, executive director of the Pennsylvania District Attorneys Association.

People are just starting to recognize that [intimate-partner violence] isn't just the victim's problem—this is a problem to society.

—Annmarie Kaiser

Heise's research showed that in many cultures, girls and boys are socialized to believe that it is not only a man's right but his responsibility to discipline his partner, sometimes physically. In her research as a member of the Defense Taskforce on Domestic Violence and author of several books, including To Have and To Hit (Chicago: Univ Illinois Pr; 1999), Jacquelyn C. Campbell, MSN, PhD, found that wife beating is almost universal. Campbell observed that most perpetrators came from cultures with an ideal of masculinity that includes ownership of one's female partner. In the United States, although male and female roles are being redefined, Campbell noted that "there is still that notion that the ideal man is very aggressive."

Glossary

Prevention

The levels of violence prevention—primary, secondary, and tertiary—are analogous to the levels of clinical prevention with which physicians are well acquainted.

Primary prevention: Clinicians define primary prevention as measures taken to prevent the onset of a condition, such as encouraging immunizations or promoting use of seatbelts. Primary prevention of violence is defined as broad efforts to address, inform, and educate the public about violence in order to encourage nonviolent behavior. This type of prevention does not just target at-risk populations but rather is an all-encompassing approach based on the idea that violence is a societal concern. Primary violence prevention focuses on fostering nonviolent problem solving and redefining role models through media messages, peer mediation, and elementary classroom education.

Secondary prevention: Early detection and treatment of at-risk populations characterize secondary violence prevention measures. Counseling of the perpetrator or mandatory attendance at first-time-offender programs may be involved. In secondary prevention, the focus is on intervening with the perpetrator before the violence becomes an entrenched pattern. According to Jacquelyn C. Campbell, MSN, PhD, secondary prevention should occur the first time a man pushes or shoves his partner. "If we wait until it's an entrenched pattern, then the criminal justice solution becomes the only viable solution," she commented. However, Campbell believes that sending this type of person to a traditional intervention program for batterers is counterproductive. "He'll say, 'I don't belong here,' and he's probably right. Most of the people who are there are court mandated to do so, and they tend to be pretty severe batterers." Lack of funding and difficulty in gauging quantifiable results are problems faced by batterer-prevention programs. Lori Heise, director of Women's Health Exchange in Washington, D.C., remarked, "The money that is available is on funding time cycles. There is a very strong emphasis on results. Unfortunately, the kind of long-term social change that primary prevention entails does not produce results in the 2-year timeframe that the donors require."

Tertiary prevention: Tertiary prevention includes treatment interventions that take place after the violence has occurred. Tertiary prevention is "damage control," and it includes the provision of counseling and other health care services to the victims. Tertiary prevention aimed at perpetrators ranges from counseling and offender programs to correction and punishment, possibly in the form of arrest and incarceration.

Domestic vs. Intimate-Partner Violence

Because the term *domestic violence* has begun to include the abuse of children, siblings, and elders, the U.S. Centers for Disease Control and Prevention prefers the more precise term *intimate-partner violence*, which it defines as actual or threatened physical or sexual, or psychological or emotional abuse by a spouse, ex-spouse, boyfriend or girlfriend, ex-boyfriend or ex-girlfriend, or date. Intimate-partner violence may include date rape, domestic abuse, spouse abuse, and battery.

Although the term *intimate-partner violence* refers to abuse by or to a man or woman, for purposes of this article, the term implies female victims and male perpetrators. According to the Report to the Nation on Crime and Justice, Bureau of Justice Statistics, in 1983, 95% of all intimate-partner violence was perpetrated against women by men. Only about 5% of intimate-partner violence is committed against U.S. men [U.S. Dept. of Justice. Violence Against Women. NCJ-145325. January 1994]).

SHIFTING THE FOCUS FROM TERTIARY TO PRIMARY PREVENTION

Harnessing all available resources strictly for treatment efforts is futile. As long as efforts do not focus on violence prevention, the cycle will continue. Kaiser said that she saw the same offenders appearing repeatedly in the court system. "Unless proper intervention occurs, you're going to have an offender again," remarked Kaiser. "[Violence] didn't just stop with one incident unless [the perpetrator] happened to get the proper counseling."

Some men are at high risk for the "cycle of violence," in which male perpetrators pass the violence onto the next generation. Men at high risk for violent behavior are those who have witnessed their mother being beaten by their father or who were a victim of abuse as a child.

In *To Have and To Hit*, Campbell found that many cultures have primary and secondary prevention models that the United States sorely lacks, in which they enact certain mechanisms as soon as physical fighting between partners begins. For example, the women of the Garifuna ethnic group in Belize will confront a man as soon as they believe he is perpetrating violence against his wife. If they hear what sounds like physical fighting in a neighboring house, the women from the village will surround the house, beckoning the woman inside to join the women. They then confront the husband by yelling things they believe will shame him, such as "How can you do something like that? It's despicable."

Experts say an effective primary prevention program for intimate-partner violence must take place at the community level, concentrating on public education and a zero-tolerance policy. Heise strongly urges a broader approach than merely counseling or incarcerating the perpetrators. Primary prevention must also include identifying at-risk populations. Heise applauds secondary prevention efforts, such as treatment programs for violent offenders, but suggests that another step, beyond just addressing the existing population of male abusers, is crucial. "We need to think about how to create a generation of men and boys who have totally different expectations about relationships." She stresses that education efforts should target the general public, including young boys and girls. "We also need to focus our attention on men in the general population"—that is, those who are not abusers—"because it's the culture at large that sanctions the behavior."

Specific Programs

Efforts to prevent violence are in their infancy, but they are beginning to grow rapidly.

The Family Violence Prevention Fund (FVPF) [www.fvpf.org], which began in San Francisco as an emergency department–based program to help abused women, is an example of an agency that focuses on prevention at all levels—primary, secondary, and tertiary. It is a national nonprofit organization whose mission is to promote education and public policy reform. It is dedicated to ending intimate-partner violence by changing the social norms that allow it to thrive. The FVPF campaign "There's No Excuse for Domestic Violence" is a case in point. This media campaign against violence takes a different approach: The intended audience of the campaign is neither the victims nor the perpetrators but, instead, the friends, coworkers, and families "who perpetuate the violence with their silence."

The National Advisory Council on Violence against Women is turning its attention to prevention efforts. The Council, established in 1995, recently issued a report entitled "Ending Violence Against Women—An Agenda for the Nation" (available at www.4woman.gov/violence/nations.htm), which addresses supporting victims of violence and preventing violence. The focus is on ending social norms that condone violence against women. The Agenda coordinates widespread efforts among key participants, including victim's advocates; the military; community leaders; organized sports; the health care, welfare, and justice systems; the media; faith communities; colleges and universities; businesses; and children's advocates. The Agenda advocates increasing the support for prevention efforts with children, including lessons about gender roles that encourage or perpetuate violence toward women.

The National Center for Injury Prevention and Control, a subagency of the National Centers for Disease Control and Prevention, started the "Family and Intimate Violence Prevention Program," which is leading efforts on community-based primary prevention programs (www.cdc.gov/ncipc/dvp/fivp/fivp.htm). The agency is involved mainly with surveillance, research, evaluation, communication, and training. The program also funds various programs focusing on all levels of prevention. For example, the program funded four multifaceted community-based projects for 5 years starting in 1994, including Milwaukee Women's Center, Inc., and Men Stopping Violence, Inc., in Georgia. It also sponsored six community-response projects, three of which were designed for rural and Native-American communities to develop a community-coordinated response to intimate-partner violence. The National Crime Prevention Council (www.ncpc.org) advocates several primary prevention programs that focus on violence in teen dating relationships. The school-based programs use trained youth to perform duties such as answering hotlines and counseling peers. One such school-based program is the "Boston Dating Violence Intervention Project," which teaches boys and girls not to accept violence in their earliest relationships. The children are taught how to manage conflict, recognize abusive behavior, and communicate respectfully.

CHILDREN AND ADOLESCENTS

More primary prevention programs are now working with children, and Campbell believes that this is an essential element of a successful primary prevention program. Educating children is an invaluable prevention effort "because it identifies a group that's at high risk and does some things very early on to mitigate that risk," Campbell remarked.

Other prevention efforts focus on adolescent dating violence. Those programs are still scarce, however, as most resources in the area of adolescent violence are channeled into prevention of peer or gang violence. Although Campbell believes these programs are highly effective, she noted that the dynamics of violence against a partner differ from those of other types of violence. Programs need to address dating violence to be an effective primary prevention tool against intimate-partner violence, Campbell suggested. "The programs for young men should address nonviolent behavior toward girls. Many men who are violent toward their partners are not violent toward anyone else."

Heise agrees with Campbell, stating that although many programs address violence in adolescents, they generally do not focus on violence between men and women. Heise noted that there are two distinctly different types of programs: One focuses on date violence but ignores all other types of violence, and the other focuses on gang violence but excludes date violence. Unfortunately, we fail to "look at all different kinds of violence as it touches young people's lives," Heise remarked. She suggested that gang violence programs should include discussions about men's roles in general and their roles as partners. Heise also suggested that primary violence prevention programs should include discussions about gender issues and what defines healthy expectations in a relationship.

Experts say an effective primary prevention program for intimate-partner violence must take place at the community level, concentrating on public education and a zero-tolerance policy.

Heise also urged that the "conspiracy of silence" be broken. "We need to be more proactive about giving young men messages that it [violence] won't be just 'behind closed doors,' that violence is not tolerated against women or within families."

Campbell's research indicates that substance abuse may be less prevalent in cases of intimate-partner abuse than is commonly believed. However, regardless of whether that can be substantiated, both problems—intimate-partner violence and substance abuse—require intervention. Campbell noted, "Just treating the substance abuse won't make the problem of violence go away."

Campbell acknowledged that programs on intimate-partner violence in the United States are moving forward, but her optimism came with reservations. "We've made a lot of progress, and I don't want to paint a bleak picture of [the United States] as being horribly sexist, because I don't think we are. I think there's less tolerance on a nationwide level for domestic violence. Nonetheless, there is still not that neighborhood ownership. I think that many people, if they saw their neighbor with a black eye, would still not reach out to her."

—Linda Gundersen

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The patient is 175 cm (69 in) tall and weighs 50 kg (110 lb). Blood pressure is 115/70 mm Hg, pulse is 96/min, and temperature is 36.9 °C (98.4 °F). The skin shows a truncal and proximal extremity rash consisting of grouped vesicles on an erythematous base. There is also evidence of excoriation. The remainder of the physical examination, including pelvic and rectal examination, is otherwise normal, and stool is negative for occult blood. The neurologic examination is normal.

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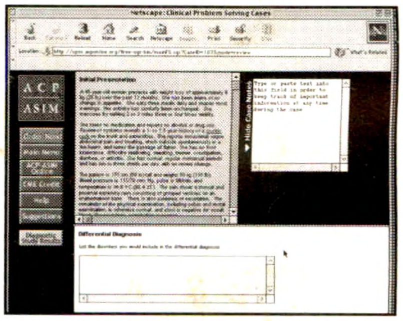

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